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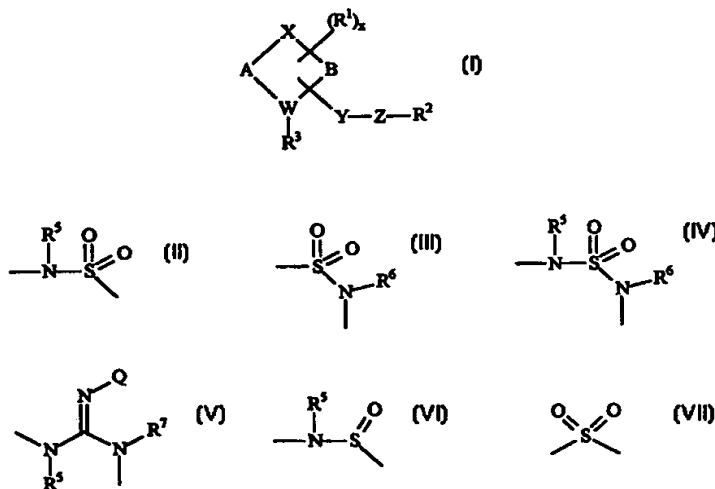
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(54) Title: HISTAMINE H₃ RECEPTOR LIGANDS**(57) Abstract**

Compounds of formula (I) (and pharmaceutically acceptable salts thereof) are histamine H₃ receptor ligands. A in the formula represents (CH₂)_m, m being from 1 to 3; B is (CH₂)_n, n being from 1 to 3; x is from 0 to 2; R¹ is C₁ to C₁₀ hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N; and up to 2 hydrogen atoms may be replaced by halogen; R² is H or C₁ to C₁₅ hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen; R³ is absent when -Y-Z-R² is attached to W, or is H or C₁ to C₇ hydrocarbyl when -Y-Z-R² is not attached to W; W is nitrogen; X is -CH₂-, -O- or -NR⁴-, R⁴ being H or C₁ to C₃ alkyl; Y replaces a hydrogen atom on any of A, B, W and X, and is C₂ to C₁₀ alkylene, in which one non-terminal carbon atom may be replaced by O; and Z is (II), (III), (IV), (V), (VI), or (VII) wherein R⁵, R⁶ and R⁷ are independently H or C₁ to C₁₅ hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R⁵ or R⁷ to form a five-membered ring or Q is linked to R² to form a six-membered ring.

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HISTAMINE H₃ RECEPTOR LIGANDS

This invention relates to compounds which bind to histamine H₃ receptors, and to methods of making such compounds.

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Histamine is well known as a mediator in certain hypersensitive reactions of the body, such as allergic rashes, hayfever and asthma. These conditions are now commonly treated with potent antagonists of histamine, so-called "antihistamines".

- 10 In the 1940s, it was noted that some physiological effects of histamine, such as increased gastric acid secretion and cardiac stimulation, were not blocked by the antihistamines which were then available. This led to the proposal that histamine receptors exist in at least two distinct types, referred to as H₁ and H₂ receptors. Subsequently, H₂ antagonists (such as cimetidine, ranitidine and famotidine) were identified, and they have become
- 15 important in the treatment of gastric ulcers.

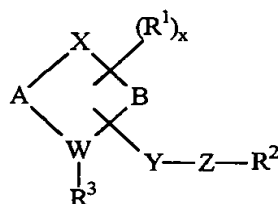
- In the early 1980s, it was established that histamine also has a role as a neurotransmitter in the central nervous system. Arrang *et al.*, Nature 302, 832 to 837 (1983), proposed the existence of a third histamine receptor subtype (H₃) located presynaptically on
- 20 histaminergic nerve endings. Arrang *et al.* postulated that the H₃ receptor is involved in inhibiting the synthesis and release of histamine in a negative feedback mechanism. The existence of the H₃ receptor was subsequently confirmed by the development of selective H₃ agonists and antagonists (Arrang *et al.*, Nature 327, 117 to 123 (1987)). The H₃ receptor has subsequently been shown to regulate the release of other neurotransmitters
- 25 both in the central nervous system and in peripheral organs, in particular in the lungs and GI tract. In addition, H₃ receptors are reported to regulate the release of histamine from mast cells and enterochromaffin-like cells.

- A need exists for potent and selective H₃ ligands (both agonists and antagonists) as tools
- 30 in the study of the role of histamine as a neurotransmitter, and in its roles as a neuro-, endo- and paracrine hormone. It has also been anticipated that H₃ ligands will have therapeutic utility for a number of indications including use as sedatives, sleep regulators, anticonvulsants, regulators of hypothalamo-hypophyseal secretion, antidepressants and

modulators of cerebral circulation, and in the treatment of asthma and irritable bowel syndrome.

A number of imidazole derivatives have been proposed in the patent literature as H₃ ligands. Representative are the disclosures of EP-A-0197840, EP-A-0214058, EP-A-0458661, EP-A-0494010, EP-A-0531219, WO91/17146, WO92/15567, WO93/01812, WO93/12093, WO93/12107, WO93/12108, WO93/14070, WO93/20061, WO94/17058, WO95/06037, WO95/11894, WO95/14007, US-A-4988689 and US-A-5217986.

10 According to the present invention, there are provided compounds of the formula



wherein

A is (CH₂)_m, m being from 1 to 3;

B is (CH₂)_n, n being from 1 to 3;

15 x is from 0 to 2;

R¹ is C₁ to C₁₀ hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R² is H or C₁ to C₁₅ hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

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R³ is absent when -Y-Z-R² is attached to W, or is H or C₁ to C₇ hydrocarbyl when -Y-Z-R² is not attached to W;

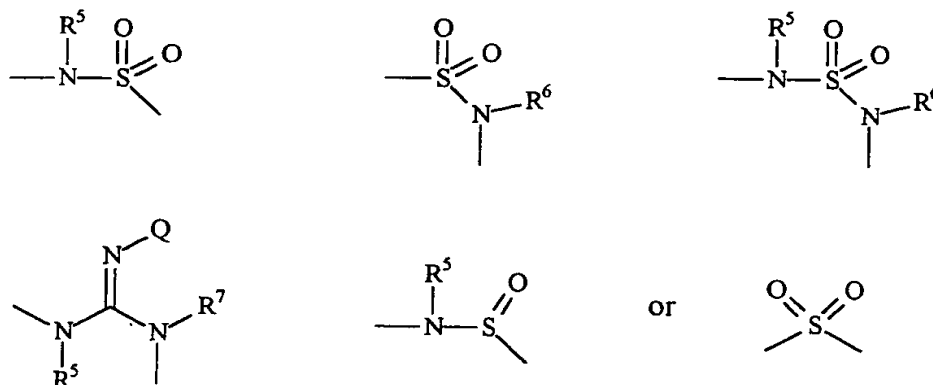
W is nitrogen;

X is -CH₂-, -O- or -NR⁴-, R⁴ being H or C₁ to C₃ alkyl;

25

Y replaces a hydrogen atom on any of A, B, W and X, and is C₂ to C₁₀ alkylene, in which one non-terminal carbon atom may be replaced by O; and

Z is



wherein R^5 , R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R^5 or R^7 to form a five-membered ring or Q is linked to R^2 to form a six-membered ring, and pharmaceutically acceptable salts thereof.

In preferred compounds according to the invention, x is 0 or 1, and more preferably 0.

- 10 R^1 , when present, is preferably selected from hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

- R^2 is preferably selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo. Particularly preferred groups for R^2 include phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

When $-Y-Z-R^2$ is not attached to W, R^3 is preferably C_1 to C_7 alkyl or benzyl.

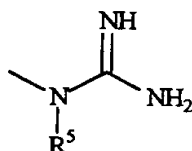
In one group of compounds according to the invention, R^5 , R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which one hydrogen atom may be replaced by halogen. R^5 , R^6 and R^7 are preferably H, aryl(C_1 to C_3)alkyl or cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

5

Y is preferably C_2 to C_{10} alkylene, and more preferably propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene.

Particularly preferred compounds according to the present invention are those in which Y is propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene, $m+n \geq 3$, $Z-R^2$ is

10



and R^5 is benzyl or halobenzyl. Such compounds, of which particular examples are given in Examples 68 to 74 below, have been found to have unusually low activity at σ_1 binding sites, in addition to high affinity at H_3 receptors.

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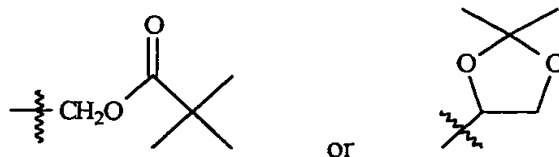
The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", Drug Delivery Systems, pp. 112-176 (1985), and Drugs, 29, pp.455-473 (1985).

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25

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-COOR^8$, wherein R^8 is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:

30



Amidated acid groups include groups of the formula $-\text{CONR}^9\text{R}^{10}$, wherein R^9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^{10} is $-\text{OH}$ or one of the groups just recited for R^9 .

5

Compounds of formula (I) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

- 10 Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, benzathine, diolamine, olamine, procaine and tromethamine.
- 15 Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate,
- 20 napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

The compounds of the invention may exist in various enantiomeric, diastereomeric and tautomeric forms. It will be understood that the invention comprehends the different

- 25 enantiomers, diastereomers and tautomers in isolation from each other, as well as mixtures of enantiomers, diastereomers and tautomers.

- The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in
- 30 both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl,

alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups. The term "hydrocarbylene" refers to corresponding divalent groups, the two free valencies being on separate atoms.

- 5 When reference is made herein to a carbon atom of a hydrocarbyl group being replaced by O, S or N, it will be understood that what is meant is that a $-\text{CH}_2-$ group is replaced by $-\text{O}-$ or $-\text{S}-$, or that a $\begin{array}{c} | \\ \text{---CH---} \end{array}$ group is replaced by a $\begin{array}{c} | \\ \text{---N---} \end{array}$ group.

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or
10 rings, which consist entirely of carbon atoms, and which may be substituted. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

15

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above, which may be substituted.

A "heterocyclic" group comprises one or more closed chains or rings which have at least
20 one atom other than carbon in the closed chain or ring, and which may be substituted. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl,
25 oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranlyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

- 30 When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy,

nitro, trihalomethyl, hydroxy, amino, C₁ to C₆ alkylamino, di(C₁ to C₆ alkyl)amino, halo, sulphamoyl and cyano.

5 The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

10

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

15 For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If
20
25 desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is
30 mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's

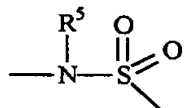
solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

5

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 $\mu\text{g/kg}$ and 50 mg/kg, especially between 10 $\mu\text{g/kg}$ and 10 mg/kg, eg. between 100 $\mu\text{g/kg}$ and 2 mg/kg.

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Compounds according to the invention wherein Z is



may be made by the reaction scheme which is illustrated in Figure 1.

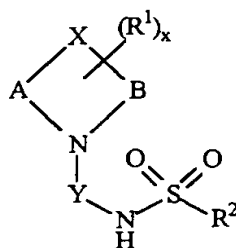
In Figure 1, the amine (1) is reacted with a sulfonyl chloride ($\text{R}^2\text{SO}_2\text{Cl}$) in the presence of a base such as triethylamine, in a suitable solvent such as dichloromethane. A reaction of this type is described in greater detail below in Example 81.

25

In Figure 1, and in a number of the other reaction schemes shown in the Figures, $\text{R}^{3\text{A}}$ represents C_1 to C_7 hydrocarbyl or a suitable protecting group such as *tert*-butoxycarbonyl. If $\text{R}^{3\text{A}}$ is a protecting group, it can be removed by conventional deprotection, and R^3 can then be introduced in the final stage by reductive amination of the secondary amine using an aldehyde of the form $\text{R}^{3\text{B}}\text{CHO}$ and sodium triacetoxyborohydride, wherein $\text{R}^{3\text{B}}$ is a homolog of the desired R^3 group having one fewer carbon atoms in the carbon chain.

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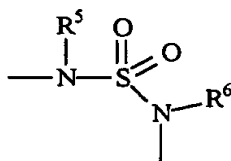
Compounds according to the invention which are of the form



may be prepared by the reaction scheme which is depicted in Figure 2. In this scheme, the amino alcohol (2) is reacted with a sulfonyl chloride of the form R^2SO_2Cl to form compound (4). This reaction is conducted in the presence of a base such as

- 5 triethylamine. A suitable solvent for the reaction is DCM. Compound (4) is then reacted with triphenylphosphine and carbon tetrachloride (preferably in a mixture with chloroform) to form the chloro derivative (5). This in turn is reacted with the cyclic imine (6) in a suitable solvent such as DCM to form the target compound (7).

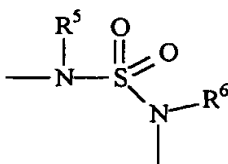
- 10 Compounds wherein Z is



may be made by the scheme illustrated in Figure 3. Chlorosulfonyl isocyanate (CSI) is first reacted with *tert*-butanol in a suitable solvent such as DCM. The reaction product (8) is then reacted with the amine (1A) in the presence of a base such as

- 15 triethylamine (and preferably in DCM as solvent) to form the N-protected sulfamide (9). This is then reacted with sodium hydride and R^2Br in a solvent such as DMF to form compound (10). When the group R^5 in the target compound (11) is hydrogen, compound (10) is simply deprotected using a suitable reagent such as trifluoroacetic acid (TFA). Example 107 below illustrates the preparation of N-(4-chlorobenzyl)-N'-
- 20 (3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide by this route. However, when the group R^5 in the target compound is other than hydrogen, compound (10) is first treated with R^5Br in the presence of a base to form compound (10A) before deprotection.

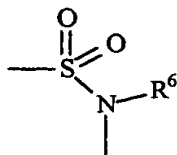
Figure 4 illustrates an alternative route for compounds wherein Z is



According to this scheme, compound (12) is reacted with the N-protected sulfamide (13) in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) in a suitable solvent such as THF. The resulting compound (14) is then deprotected in conventional fashion to provide the target compound (15), if the group R⁶ in the target compound is hydrogen. If R⁶ is not hydrogen, compound (14) is reacted with R⁶Br in the presence of a base to form compound (14A) before the deprotection step. This reaction scheme is further illustrated by Example 108 below.

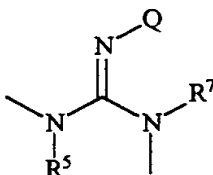
In some cases, N-substituted forms of the compound (15) may also be obtained by the reaction shown in Figure 5. In this procedure, which is exemplified in Example 135 below, the amine (1) is reacted with sulfamide (16) and an amine of the form R²R⁶NH.

Figure 6 illustrates a scheme for preparing compounds wherein Z is



In this scheme, Y² represents a bond or a C₁ to C₈ alkylene group. Dimethylsulfoxide is first added to oxalyl chloride (in a suitable solvent such as DCM) at reduced temperature. Compound (17), containing a free hydroxyl group, is then added, followed by a base such as triethylamine. The resulting aldehyde (18) is then reacted with the N-protected methyl sulfonamide (19) to yield compound (20). The N-protected methyl sulfonamide (19) is suitably prepared by reaction of an amine of the form R²NH₂ with mesyl chloride, followed by *tert*-butoxycarbonyl protection. Compound (20) is then reduced (e.g. by hydrogenation in the presence of a palladium-on-charcoal catalyst) to form the target compound (21) in which R⁶ is hydrogen. Example 136 below illustrates a synthesis by this route. If R⁶ is to be other than hydrogen, compound (21) is reacted with R⁶Br in the presence of a base to form compound (21A).

Figure 7 illustrates a scheme for preparing compounds wherein Z is

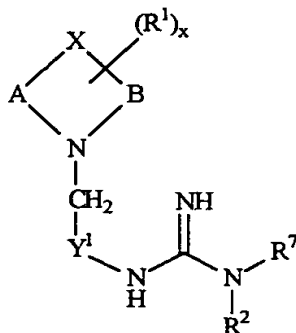


According to this scheme, the amine (1) is reacted with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) in a suitable solvent such as THF. The resulting N-protected guanidine (23) is then deprotected using any appropriate means, such as hydrogen chloride-dioxan, to yield the target compound (24) in which R^7 is hydrogen. If R^7 in the target compound is other than hydrogen, compound (23) is reacted with $R^7\text{Br}$ in the presence of a base to yield compound (23A) before the deprotection step. An illustrative synthesis of this type is given below in Example 1.

Figure 8 illustrates a suitable route for the preparation of guanidine derivatives wherein R^2 is other than hydrogen. According to this scheme, compound (22) is first reacted with sodium hydride (in a suitable solvent such as DMF), and then with a compound of the form $R^2\text{Br}$ to yield the guanidine derivative (25). This is then reacted with the amine (1), and subsequently deprotected, in a manner analogous to that shown in Figure 7. A preparation of this type is illustrated in Example 2 below.

Compound (25) may alternatively be derived from compound (22) by reaction with an alcohol of the form $R^2\text{OH}$ in the presence of triphenylphosphine and DEAD, preferably in THF as solvent. This variation is illustrated in Example 3 below.

An alternative route for the preparation of compounds of the form



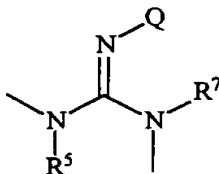
(in which Y^1 represents a C_1 to C_9 alkylene group) is illustrated in Figure 9. As shown in Figure 9, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) is reacted with an enol of the form $\text{HO}-Y^1-\text{CH}=\text{CH}_2$ in the presence of triphenylphosphine and

DEAD. The resulting compound (26) is then reacted with $R^2R^7NH_2$ to provide compound (27), which is subsequently converted to the corresponding aldehyde (28) by treatment first with ozone and then with methylsulfide. Reaction of the aldehyde with the cyclic imine (29) in the presence of triacetoxyborohydride then affords the compound (30), from which the target compound (31) may be obtained by conventional deprotection methods. A synthesis of this type is illustrated in Example 17 below.

Compounds according to the invention in which Z is a sulfinamide moiety may be prepared by the reaction scheme illustrated in Figure 10. According to this scheme, the thiol compound R^2SH (32) is reacted with N-bromosuccinimide in methanol, to provide the sulfinic acid ester (33). This is then reacted with the amine (1) and lithium diisopropylamide to provide the target compound (34). Example 87 below provides further details of this preparative method.

Compounds in which Z is a sulfone group may be prepared by the method shown in Figure 11, in which Y^1 represents a C_1 to C_9 alkylene group. In this method, sodium hydride is added to the thiol compound R^2SH (32), followed by an appropriate ester (e.g. the ethyl ester) of an acid of the form $Br-Y^1-COOH$ (35), to form the sulfanyl compound (36). This is then oxidised (e.g. with *meta*-chloroperoxybenzoic acid) to the corresponding sulfonyl compound (37). Appropriate reduction (e.g. with lithium aluminium hydride) then provides the alcohol (38), which in turn is oxidised to the aldehyde (39) using a reagent such as sulfur trioxide-pyridine. Finally, this is then reacted with the cyclic imine (6) under conditions analogous to those described above with reference to Figure 9. A synthesis of this type is illustrated in Example 88 below.

Figures 12 to 16 illustrate further routes for preparing compounds according to the invention wherein Z is



According to Figure 12, the N-protected amine (40) is alkylated with an appropriate alkene to form trisubstituted amine (40A). This is deprotected and guanylated to yield

guanidine derivative (41). Depending on the desired degree of N-substitution, guanidine derivative (41) can be treated in either of the following two ways. In one method, guanidine derivative (41) is alkylated with an appropriate alkylating agent and then oxidised by ozonolysis to yield aldehyde (42), which is reductively aminated and
5 deprotected to yield target compound (43). Alternatively, guanidine derivative (41) is oxidised by ozonolysis without prior alkylation to yield aldehyde (44), which is similarly reductively aminated and deprotected to yield target compound (45).

A further route to target compound (45) is to reverse the order of guanylation and
10 ozonolysis/ reductive amination. Hence trisubstituted amine (40A) is ozonolysed, reductively aminated and deprotected to form amine (40B). This is then guanylated and deprotected to yield target compound (45). This synthesis is illustrated in Example 68 below.

15 According to Figure 13, disubstituted amine (46) is guanylated to yield N-protected guanidine (47), which is alkylated with an appropriate alkylating agent, preferably a dibromide. The resulting compound (48) is aminated with an appropriate amine and deprotected to form target compound (49). Example 50 illustrates this synthesis.

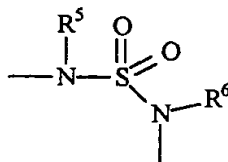
20 According to Figure 14, the acid chloride (50) is acylated with an appropriate aminoalcohol. The hydroxy group of the resulting amide (51) is tosylated and then substituted by amination with an appropriate amine to yield amide (52). The carbonyl group of the amide (52) is then fully reduced to form amine (53), which is guanylated and deprotected to yield target compound (54). This synthesis is illustrated by
25 Example 77.

According to Figure 15, the N-protected amine (40) is alkylated with an appropriate alkylating agent to yield substituted amine (55), in which L represents a leaving group such as bromine. This is reacted with the appropriate cyclic amine to yield compound
30 (56), which is then deprotected and guanylated to form protected target compound (57). Finally, compound (57) is fully deprotected to yield target compound (58). Example 69 below provides an illustration of this synthesis.

According to Figure 16, an appropriate amine is reacted with isothiocyanate (59) to yield thiourea (60), which is then S-alkylated by the addition of iodomethane. The resulting thiourea derivative (61) is substituted by an appropriate amine to yield target compound (62). This synthesis is illustrated by Example 19.

5

Figure 17 illustrates an alternative route for compounds wherein Z is



According to this scheme, N-protected sulfamide (13) is alkylated with an appropriate alcohol (63), yielding a mixture of mono- and dialkylated sulfamides (64A/B). These are then ozonolysed to form aldehydes (65A/B), which are reductively aminated to yield target compounds (66A/B). It will be understood that the desired sulfamide (64A or 64B) may be separated from the mixture (64A/B) before ozonolysis, or a mixture of aldehydes (65A/B) may be formed, with subsequent purification of the desired species. Examples 139-141 below provide further details of this preparative method.

15

EXPERIMENTAL

¹H NMR were recorded on a Bruker DRX-300 at 300MHz, the chemical shifts were recorded relative to an internal standard and all coupling constants where given are reported in hertz as the final number following multiplicity information. All spectra were obtained in deuteriochloroform unless otherwise noted. Flash column chromatography was performed on Merck silica gel 60 using the reported solvent systems. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl under argon and distilled prior to use. Dichloromethane (DCM) was dried over calcium hydride and distilled prior to use. Commercially available anhydrous N,N-dimethylformamide (DMF) was used without further purification. Commercially available hydrogen chloride in 1,4-dioxan (4M) was used to prepare hydrochloride salts as described. All reactions were carried out under a positive pressure of dry argon. All microanalyses are quoted as percentages.

30

Example 1*N*-(3-Pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride**Step a** *N,N'*-Bis(tert-butoxycarbonyl)-*N''*-(3-pyrrolidin-1-yl-propyl)-guanidine. A

solution of 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (580mg,
5 2.00mmol) and 3-pyrrolidin-1-yl-propylamine (665mg, 5.19mmol) in THF (20ml) and
water (2ml) was heated at reflux for 1h. The solvent was evaporated at reduced
pressure and the residue partitioned between ethyl acetate (50ml) and water (50ml).
The aqueous phase was discarded and the organic phase was washed with brine (50ml)
and then dried over anhydrous sodium sulfate. The filtrate was evaporated and the
10 residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia)
to obtain the title compound (718mg, 97%). ¹H NMR 11.49 (1H, br s), 8.72 (1H, br
s), 3.54-3.48 (2H, m), 2.57-2.52 (6H, m), 1.79-1.72 (6H, m), 1.51 (9H, s), 1.50 (9H, s).

Step b *N*-(3-Pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

To a solution of the product from step a (718mg, 1.94mmol) in 1,4-dioxan (5ml) was
15 added a solution of hydrogen chloride in 1,4-dioxan (4M, 4ml, 16mmol). The
resultant solution was stirred at ambient temperature for 16h to give a pink suspension.
The solid was removed by filtration and dried *in vacuo* at 50°C. The solid was
dissolved in aqueous hydrochloric acid (1M, 10ml) and the resultant solution was
heated at reflux for 1h. The solvent was removed at reduced pressure and the residue
20 evaporated from ethanol (10ml), chloroform (10ml) and ether (10ml) to give the title
compound. ¹H NMR (DMSO-*d*₆) 11.04 (1H, br s), 8.00 (1H, t, 6), 7.54-7.12 (4H, br
m), 3.53-3.39 (2H, m), 3.28-3.21 (2H, m), 3.16-3.09 (2H, m), 3.01-2.93 (2H, m), 2.00-
1.86 (6H, m). Microanalysis found C 37.78 H 8.44 N 22.64. C₈H₂₀Cl₂N₄·0.48H₂O
requires C 38.16 H 8.39 N 22.25.

Example 2*N*-(4-Chlorobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride**Step a** 1,3'-Bis(tert-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea.

To an ice-cooled solution of 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea
30 (1.00g, 3.45mmol) in DMF (10ml) was added sodium hydride (60% dispersion in
mineral oil, 167mg, 4.18mmol) in a single portion. The resultant suspension was
stirred at this temperature for 1h and then treated in a single portion with 4-
chlorobenzyl bromide (780mg, 3.80mmol). The cooling bath was removed and the
reaction mixture was stirred at ambient temperature for 16h. Water (50ml) was added

and the aqueous phase was extracted with ethyl acetate (50ml). The aqueous phase was discarded and the organic phase washed twice with brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (9:2 hexane:ethyl acetate) to give the title compound (987mg, 69%). ¹H NMR 7.30 (4H, s), 4.74 (2H, s), 2.31 (3H, s), 1.53 (9H, s), 1.42 (9H, s).

Step b *N,N'*-Bis(*tert*-butoxycarbonyl)-*N'*-(4-chlorobenzyl)-*N''*-(3-pyrrolidin-1-yl-propyl)-guanidine. The title compound was prepared as in Example 1 step a with the product from Example 2 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ¹H NMR 7.27 (4H, br s), 4.78 (2H, s), 3.16 (2H, m), 2.43-2.37 (6H, br s), 1.76 (4H, m), 1.57-1.50 (2H, m), 1.50 (9H, s), 1.43 (9H, s).

Step c *N*-(4-Chlorobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride. A solution of the product of step b (1.14g, 2.00mmol) in 1,4-dioxan (5ml) was treated with hydrogen chloride in 1,4-dioxan (15ml) and the reaction mixture stirred at

ambient temperature for 16h. The solvent was evaporated at reduced pressure. The residue was evaporated from DCM (30ml) to give the title compound (700mg, 95%). ¹H NMR (DMSO-*d*₆) 10.97 (1H, br s), 8.29 (1H, br s), 8.07 (1H, t, 6), 7.69 (2H, br s), 7.40 (2H, d, 8.4), 7.30 (2H, d, 8.4), 4.37 (2H, s), 3.48-3.45 (2H, m), 3.24-3.20 (2H, m), 3.08-3.03 (2H, m), 2.94-2.91 (2H, m), 2.00-1.84 (6H, m). Microanalysis found C 48.91 H 6.95 N 14.99. C₁₅H₂₅Cl₃N₄ requires C 48.99 H 6.85 N 15.24.

Example 3

N-(4-Methoxybenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

Step a 1,3'-Bis(*tert*-butoxycarbonyl)-1-(4-methoxybenzyl)-2-methyl-2-thiopseudourea.

To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.45g, 5.00mmol), 4-methoxybenzyl alcohol (759mg, 5.50mmol) and triphenylphosphine (1.97g, 5.50mmol) in THF (20ml) was added diethylazodicarboxylate (1.286ml, 5.50mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue purified by flash column chromatography (90:10 hexane:ethylacetate) to give the title compound (1.105g, 54%). ¹H NMR 7.30-7.27 (2H, m), 6.87-6.84 (2H, m), 4.71 (2H, s), 3.80 (3H, s), 2.27 (3H, s), 1.53 (9H, s), 1.44 (9H, s).

Step b *N,N'*-Bis(*tert*-butoxycarbonyl)-*N'*-(4-methoxybenzyl)-*N''*-(3-pyrrolidin-1-yl-propyl)-guanidine. The title compound was prepared as in Example 1 step a with the product from Example 3 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ¹H NMR 10.00-9.50 (1H, br s), 7.27-7.22 (2H, m), 6.82-6.80 (2H, m), 4.73 (2H, s), 3.77 (3H, s), 3.09 (2H, br s), 2.40 (4H, br s), 2.31 (2H, br m), 1.73 (4H, s), 1.49 (9H, s), 1.42 (9H, s).

Step c *N*-(4-Methoxybenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-

hydrochloride. The title compound was prepared as in Example 2 step c with the product of Example 3 step b replacing the product of Example 2 step b. ¹H NMR

(DMSO-*d*₆) 11.00 (1H, br s), 8.25 (1H, br s), 8.11 (1H, t, 6), 7.71 (2H, br s), 7.29 (2H, d, 8.4), 6.93 (2H, d, 8.4), 4.36 (2H, s), 3.73 (3H, s), 3.55-3.26 (4H, m), 3.07 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 49.30 H 8.19 N 14.17.

C₁₆H₂₈Cl₂N₄O·1.5H₂O requires C 49.23 H 8.00 N 14.35.

Example 4

N-Naphthalen-2-yl-methyl-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 2-(bromomethyl)naphthalene replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.00 (1H, br s), 8.39 (1H, br s), 8.13 (1H, br s), 7.94-7.85 (4H, m), 7.75 (2H, br s), 7.53-7.46 (3H, m), 4.62 (2H, d, 6), 3.48-3.32 (4H, m), 3.08-3.06 (2H, m), 2.87 (2H, s), 1.93-1.84 (6H, m). Microanalysis found C 56.89 H 7.60 N 13.95. C₁₇H₂₈Cl₂N₄·H₂O requires C 56.86 H 7.53 N 13.96.

Example 5

N-(4-(Trifluoromethyl)benzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 1-bromomethyl-4-

trifluoromethyl-benzene replacing 4-chlorobenzyl bromide in step a. ¹H NMR

(DMSO-*d*₆) 11.06 (1H, br s), 8.47 (1H, br s), 8.21-8.18 (1H, br m), 7.77-7.73 (4H, m), 7.57 (2H, d, 9), 4.58 (2H, d, 6), 3.49-3.44 (2H, m), 3.35-3.29 (2H, m), 3.13-3.07 (2H, m), 2.94 (2H, br s), 1.96-1.88 (6H, m). Microanalysis found C 52.24 H 6.92 N 15.41.

C₁₆H₂₅Cl₂N₄F₃ C 52.53 H 6.89 N 15.31.

Example 6*N*-(4-Iodobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 4-iodobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.04 (1H, br s), 8.32 (1H, br s), 8.13 (1H, t, 6), 7.75-7.72 (4H, m), 7.17 (2H, d, 9), 4.41 (2H, d, 6), 3.49-3.44 (2H, m), 3.31-3.29 (2H, m), 3.09-3.06 (2H, m), 2.93-2.92 (2H, br m), 1.97-1.86 (6H, m). Microanalysis found C 34.05 H 6.14 N 10.42. C₁₅H₂₅Cl₂N₄I·4H₂O C 33.91 H 6.26 N 10.55.

10 **Example 7** *N*-(3-Bromo-4-methoxy-benzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with (3-bromo-4-methoxy-phenyl)-methanol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.28 (1H, br s), 8.07 (1H, t, 6), 7.70 (2H, br s), 7.58 (1H, d, 2.1), 7.36-7.33 (1H, m), 7.12 (1H, d, 8.4), 4.37 (2H, s), 3.83 (3H, s), 3.48-3.29 (4H, m), 3.10-3.08 (2H, m), 2.96-2.93 (2H, s), 1.97-1.84 (6H, m). Microanalysis found C 43.09 H 6.33 N 12.38. C₁₆H₂₇Cl₂N₄OBr requires C 43.45 H 6.15 N 12.67.

Example 8

20 *N*-Benzyl-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with benzyl bromide replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.10 (1H, br s), 8.36 (1H, br s), 8.16 (1H, s), 7.76 (2H, br s), 7.39-7.26 (5H, m), 4.37 (2H, d, 6), 3.47-3.27 (4H, m), 3.10-2.92 (4H, m), 1.96-1.86 (6H, m). Microanalysis found C 54.09 H 7.90 N 16.71. C₁₅H₂₆Cl₂N₄ requires C 54.05 H 7.86 N 16.81.

Example 9*N*-(4-Bromobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 4-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 10.92 (1H, br s), 8.26 (1H, br s), 8.03 (1H, br s), 7.68 (2H, br s), 7.56 (2H, d, 9), 7.28 (2H, d, 9), 4.40-4.42 (2H, m), 3.52-3.46 (2H, m), 3.37-3.10 (2H, m), 3.11-2.94 (4H, m), 1.93-1.86 (6H, m).

Example 10

N-(3-Bromobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 3-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.32 (1H, br s), 8.08 (1H, br s), 7.72 (2H, br s), 7.55-7.47 (2H, m), 7.35-7.29 (2H, m), 4.45-4.44 (2H, m), 3.47-3.30 (4H, m), 3.13-3.08 (2H, br s), 2.96 (2H, br s), 1.94-1.87 (6H, m). Microanalysis found C 38.59 H 6.72 N 12.06. C₁₅H₂₅BrCl₂N₄·3H₂O requires C 38.64 H 6.70 N 12.02.

Example 11

N-(2-Bromobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 2-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.11 (1H, br s), 8.17 (2H, br s), 7.79 (2H, br s), 7.67-7.64 (1H, m), 7.43-7.25 (3H, m), 4.53-4.44 (2H, m), 3.50-3.45 (2H, m), 3.31 (2H, m), 3.17-3.11 (2H, m), 2.99-2.95 (2H, m), 1.97-1.88 (6H, m). Microanalysis found C 38.46 H 6.42 N 12.10. C₁₅H₂₅BrCl₂N₄·3H₂O requires C 38.64 H 6.70 N 12.02.

Example 12

N-Biphenyl-4-yl-methyl-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.33 (1H, br s), 8.1 (1H, br s), 7.75 (2H, br s), 7.69-7.65 (4H, m), 7.49-7.36 (5H, m), 4.49 (2H, m), 3.50-3.46 (2H, m), 3.32 (2H, m), 3.14-3.09 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 56.80 H 7.87 N 12.88. C₂₁H₃₀Cl₂N₄·2H₂O requires C 56.63 H 7.69 N 12.58.

Example 13

N-(1*H*-Benzimidazol-5-yl-methyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine tris-hydrochloride.

Step a 1*H*-Benzimidazole-5-carboxylic acid methyl ester hydrochloride. Hydrogen chloride gas was bubbled through an ice-cooled suspension of 5-benzimidazole carboxylic acid (8.11g, 50.0mmol) in methanol (150ml) for 30 minutes. The resultant suspension was heated at reflux for 4h to give a dark brown solution. The solution

was allowed to cool to ambient temperature and then further cooled in an ice-bath.

The resulting solid was collected by vacuum filtration and washed with ether to give the title compound (11.6g, 100%). ¹H NMR (DMSO-*d*₆) 9.59 (1H, s), 1H, d, 0.3), 8.12-8.09 (1H, m), 7.96-7.93 (1H, m), 3.91 (3H, s).

- 5 **Step b** *1-Trityl-1H-Benzimidazole-5-carboxylic acid methyl ester*. To a solution of the product of step a (11.6g, 50mmol) and triethylamine (21.0ml, 151mmol) in chloroform (150ml) was added portionwise trityl chloride (15.33mmol). The solution was stirred at ambient temperature for 48h. The organic solution was washed sequentially with water (100ml), 10% aqueous citric acid (100ml) and brine (100ml). The organic phase
10 was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (4:1 DCM:ethyl acetate) to afford the title compound (10.47g, 46%).

- Step c** *1-Trityl-1H-benzimidazol-5-yl-methanol*. To an ice-cooled stirred suspension of the product of step b (3.61g, 7.94mmol) in THF (30ml) was added dropwise a solution
15 of lithium aluminium hydride (1.0M in THF, 10ml, 10.0mmol). The suspension was stirred at this temperature for 1h and then was quenched with saturated aqueous ammonium chloride (100ml). The aqueous solution was extracted thrice with ethyl acetate (100ml) and the combined organic phases were washed with brine (200ml). The organic phase was dried over magnesium sulfate and the filtrate was evaporated at
20 reduced pressure and the residue recrystallised from ethyl acetate/hexane to afford the title compound (2.68g, 79%). ¹H NMR 7.89 (1H, s), 7.74 (1H, d, 8.4), 7.33-7.17 (17H, m), 6.44 (1H, d, 0.9), 4.45 (2H, d, 6), 1.37 (1H, t, 6).

Step d. *N-(1H-Benzimidazol-5-yl-methyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine tris-hydrochloride*.

- 25 The title compound was prepared as in Example 3 with the product from Example 13 step c replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.01 (1H, br s), 9.59 (1H, br s), 8.55 (1H, br s), 8.21 (1H, br s), 7.88-7.80 (4H, m), 7.56 (2H, d, 9), 4.64 (2H, d, 6), 4.0-3.5 (1H, br s), 3.51-3.44 (2H, m), 3.38-3.29 (2H, m), 3.14 (2H, m), 2.97-2.92 (2H, m), 1.97-1.87 (6H, m). Microanalysis found C 41.24 H 7.40 N
30 18.22. C₁₆H₂₇Cl₃N₆·3H₂O requires C 41.43 H 7.17 N 18.12.

Example 14

4-(N'-(3-Pyrrolidin-1-yl-propyl)-guanidinomethyl)-benzoic acid methyl ester bis-hydrochloride.

The title compound was prepared as in Example 2 with 4-bromomethyl-benzoic acid methyl ester replacing 4-chlorobenzyl bromide in step a. ¹H NMR (DMSO-*d*₆) 11.01 (1H, br s), 8.37 (1H, br s), 8.12 (1H, br s), 7.95 (2H, d, 9), 7.74 (2H, br s), 7.45 (2H, d, 9), 4.53 (2H, d, 6), 3.84 (3H, s), 3.48-3.46 (2H, m), 3.31 (2H, m), 3.12-3.08 (2H, m), 2.96-2.94 (2H, m), 1.96-1.85 (6H, m). Microanalysis found C 48.92 H 7.66 N 13.38. C₁₇H₂₈Cl₂N₄O₂-1.5H₂O requires C 48.81 H 7.47 N 13.39.

Example 15

N-(4-Chlorobenzyl)-*N'*-(3-morpholin-4-yl-propyl)-guanidine bis-hydrochloride.

10 A solution of the product from Example 2 step a (535mg, 1.29mmol) and 4-(3-aminopropyl)-morpholine (0.425ml, 2.91mmol) in THF (10ml) and water (1ml) was heated at reflux for 1h. The reaction was partitioned between ethyl acetate (40ml) and water (40ml) and the aqueous phase was discarded. The organic phase was washed with brine (50ml) and dried over anhydrous sodium sulfate. The filtrate was
15 evaporated at reduced pressure and the residue purified by flash column chromatography (120:10:1 DCM:methanol:ammonia). The residue was dissolved in chloroform (5ml) and treated with hydrogen chloride in 1,4-dioxan (5ml) and the solution stirred at ambient temperature for 18h. The solvent was removed at reduced pressure and the residue suspended in 1,4-dioxan (10ml). Filtration of the suspension
20 afforded the title compound (120mg, 24%). ¹H NMR (DMSO-*d*₆) 11.20 (1H, s), 8.28 (1H, s), 8.05 (1H, br s), 7.70 (2H, br s), 7.43 (2H, d, 8.4), 7.34 (2H, d, 8.4), 4.42 (2H, d), 4.00-3.79 (4H, m), 3.39-3.35 (6H, m), 3.11-2.99 (2H, m), 1.98-1.91 (2H, m). Microanalysis found C 47.06 H 6.63 N 13.39 C₁₅H₂₅Cl₃N₄O-0.28 1,4-dioxan requires C 47.41 H 6.72 N 13.71.

25

Example 16

N-(4-Chlorobenzyl)-*N'*-(2-pyrrolidin-1-yl-ethyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 2-pyrrolidin-1-yl-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 11.03 (1H, br s), 8.47 (1H, br s), 8.21 (1H, br s), 7.87 (2H, br s), 7.54-7.28 (4H, m), 4.49 (2H, d, 6), 3.68-3.30 (6H, m), 3.05-2.99 (2H, m), 2.01-1.87 (4H, m). Microanalysis found C 46.84 H 6.62 N 15.72. C₁₄H₂₃Cl₃N₄-0.25H₂O requires C 46.94 H 6.61 N 15.64.

Example 17

N-(4-Chlorobenzyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a *1,3'*-Bis(*tert*-butoxycarbonyl)-1-(1-pent-4-enyl)-2-methyl-2-thiopseudourea.

The title compound was prepared as in Example 3 step a with 4-penten-1-ol replacing

5 4-methoxybenzyl alcohol. ¹H NMR 5.88-5.74 (1H, m), 5.08-4.97 (2H, m), 3.54-3.49 (2H, m), 2.39 (3H, s), 2.11-2.04 (2H, m), 1.83-1.70 (2H, m), 1.51 (9H, s), 1.49 (9H, s).

Step b *N,N'*-Bis(*tert*-butoxycarbonyl)-*N'*-(4-chlorobenzyl)-*N''*-(1-pent-4-enyl)-guanidine. A solution of the product from step a (1.56g, 4.36mmol) and 4-

10 chlorobenzylamine (1.20ml, 9.83mmol) in THF (20ml) and water (2ml) was heated at reflux for 24h. The solution was diluted with ethyl acetate (30ml) and washed sequentially with water (30ml), 10% aqueous citric acid (30ml) and brine (30ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (4:1 hexane:ethyl acetate) to give the title compound (1.464g, 74%). ¹H NMR 7.36-7.23
15 (4H, m), 5.82-5.73 (1H, m), 5.03-4.96 (2H, m), 4.40 (2H, br s), 3.68 (2H, bt, 7.2), 2.08-2.01 (2H, m), 1.68-1.54 (2H, m), 1.49 (9H, s), 1.48 (9H, s).

Step c *N,N'*-Bis(*tert*-butoxycarbonyl)-*N'*-(4-chlorobenzyl)-*N''*-(1-butan-4-yl)-

guanidine. Ozone gas was bubbled through a solution of the product from step b (500mg, 1.11mmol) in methanol (10ml) at -78°C for 5 minutes. The blue solution was

20 purged of colour with nitrogen and then treated at this temperature with methylsulfide (0.81ml, 11.0mmol). The reaction mixture was allowed to warm to ambient temperature and stirred at this temperature for 2h. The solvent was evaporated at reduced pressure and the residue was purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the title compound (403mg, 80%). ¹H NMR 9.75 (1H,
25 s), 9.5 (1H, br s), 7.34 (2H, d, 8.4) 7.24 (2H, d, 8.4), 4.40 (2H, s), 3.70 (2H, t, 7.2), 2.48 (2H, t, 7.2), 1.93-1.83 (2H, m), 1.54 (9H, s), 1.49 (9H, s).

Step d *N,N'*-Bis(*tert*-butoxycarbonyl)-*N'*-(4-chlorobenzyl)-*N''*-(4-pyrrolidin-1-yl-butyl)-*guanidine*. To an ice cooled suspension of the product of step c (400mg,

0.88mmol) and pyrrolidine (0.080ml, 0.96mmol) in 1,2-dichloroethane (3ml) was
30 added in a single portion sodium triacetoxymethylborohydride (280mg, 1.32mmol). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (30ml) and extracted twice with ethyl acetate (20ml). The combined organic phases were dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced

pressure. The residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to give the title compound (389mg, 87%). ¹H NMR 9.50 (1H, br s), 7.33 (2H, d, 7.8), 7.24 (2H, d, 7.8), 4.42-4.41 (2H, m), 3.68 (2H, m), 2.51 (6H, br s), 1.78 (4H, m), 1.69-1.55 (4H, m), 1.49 (9H, s), 1.48 (9H, s).

5 **Step e** *N*-(4-Chlorobenzyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 step c. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.26 (1H, br s), 8.03 (1H, br s), 7.64 (2H, m), 7.24 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.49-3.44 (2H, m), 3.20-3.16 (2H, m), 3.11-3.06 (2H, m), 2.95-2.91 (2H, m), 1.97-1.86 (4H, m), 1.73-1.63 (2H, m), 1.56-1.49 (2H, m). Microanalysis
10 found C 46.89 H 7.49 N 13.53. C₁₆H₂₇Cl₃N₄·0.61H₂O requires C 46.78 H 7.42 N 13.64.

Example 18

N-(4-Chlorobenzyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.

15 The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.28 (1H, br s), 8.00 (1H, br s), 7.64 (2H, m), 7.42 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.50-3.45 (2H, m), 3.20-3.13 (2H, m), 3.06-2.93 (4H, m), 1.97-1.86 (4H, m), 1.71-1.61 (2H, m), 1.53-1.43 (2H, m), 1.35-1.28 (2H, m). Microanalysis found C 48.33 H 7.59 N 13.30.
20 C₁₇H₂₉Cl₃N₄·1.57H₂O requires C 48.15 H 7.64 N 13.21.

Example 19

N-(4-Chlorophenyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine.

Step a *N*-(4-Chlorophenyl)-thiourea. To stirred aqueous ammonia (880, 20ml) was
25 added dropwise with ice-cooling a solution of 4-chlorophenylisothiocyanate (3.39g, 20.0mmol) in 1,4-dioxan (20ml). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The solid was removed by filtration and the filter-cake washed with water (50ml). The title compound was dried *in vacuo* (50°C) for 16h and isolated as a white solid (2.90g, 78%). ¹H NMR (DMSO-*d*₆) 9.72
30 (1H, br s), 7.61-7.32 (6H, br m).

Step b *1*-(4-Chlorophenyl)-2-methyl-2-thiopseudourea hydroiodide. To a solution of the product of step a (2.82g, 15.11mmol) in acetone (30ml) was added iodomethane (1.41ml, 22.65mmol) and the resultant reaction mixture was heated at reflux for 1h. The solvent was removed at reduced pressure and the residue suspended in ethyl

acetate (50ml). The solid was removed by filtration and the filter-cake washed with ethyl acetate (50ml) to give the title compound as a white solid (4.53g, 91%). ¹H NMR (DMSO-*d*₆) 11-9 (3H, br s), 7.57 (2H, d, 8.7), 7.36 (2H, d, 8.7), 2.68 (3H, s).

Step c *N*-(4-Chlorophenyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine. A solution of the product of step b (986mg, 3.00mmol) and *N*-(3-aminopropyl)-pyrrolidine (0.948ml, 7.50mmol) in ethanol (10ml) was heated at reflux for 16h. The solvent was removed at reduced pressure and the residue suspended in aqueous ammonia (880, 25ml). The solid was removed by filtration and the filter-cake washed sequentially with water (50ml) and diethyl ether (50ml) to give the title compound as a white solid (585mg, 69%). ¹H NMR (DMSO-*d*₆) 7.18-7.12 (2H, m), 6.76-6.66 (2H, m), 5.8-4.8 (3H, br s), 3.12 (2H, t, 6.9), 2.43-2.36 (6H, m), 1.69-1.56 (6H, m). Microanalysis found C 60.01 H 7.62 N 19.74. C₁₄H₂₁ClN₄ requires C 59.88 H 7.54 N 19.95.

Example 20

N-(2-(4-Chlorophenyl)ethyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-(4-chlorophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.04 (1H, br s), 7.92 (1H, br s), 7.80 (1H, br s), 7.59 (2H, br s), 7.38-7.30 (4H, m), 3.50-3.23 (6H, m), 3.11-3.08 (2H, m), 2.98-2.92 (2H, m), 2.79 (2H, t, 7.5), 2.00-1.82 (6H, m). Microanalysis found C 50.31 H 7.17 N 14.41. C₁₆H₂₇Cl₃N₄ requires C 50.34 H 7.13 N 14.68.

Example 21

N-(3-(4-Chlorophenyl)propyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 3-(4-chlorophenyl)-propanol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.92 (2H, br s), 7.58 (2H, m), 7.32 (2H, d, 9), 7.24 (2H, d, 9), 3.49-3.47 (2H, m), 3.25 (2H, m), 3.17-3.12 (4H, m), 2.99-2.77 (2H, br m), 2.63 (2H, t, 7.5), 1.97-1.71 (8H, m). Microanalysis found C 51.28 H 7.43 N 13.84. C₁₇H₂₉Cl₃N₄ requires C 51.59 H 7.39 N 14.16.

Example 22

N-(4-Phenylbutyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 4-phenyl-butan-1-ol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.07 (1H, br s), 7.92 (1H, br s), 7.84 (1H, br s), 7.57 (2H, br s), 7.29-7.13 (5H, m), 3.51-3.46 (2H, m), 3.28-3.26 (2H, m), 3.17-3.11 (4H, m), 2.98-2.96 (2H, m), 2.61-2.56 (2H, m), 1.97-1.84 (6H, m), 1.65-1.42 (4H, m). Microanalysis found C 52.70 H 8.77 N 13.43. C₁₇H₃₂Cl₂N₄·2H₂O requires C 52.55 H 8.82 N 13.62.

Example 23

N-(2-(4-Chlorophenyl)ethyl)-*N'*-(2-pyrrolidin-1-yl-ethyl)-guanidine bis-hydrochloride.

The title compound was prepared as in example 3 with 2-(4-chlorophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a, and 2-pyrrolidin-1-yl-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.97 (1H, br s), 7.94 (1H, br s), 7.86 (1H, br s), 7.68 (2H, br s), 7.38-7.31 (4H, m), 3.59-3.22 (8H, m), 3.00-2.99 (2H, m), 2.81 (2H, t, 6), 1.99-1.87 (4H, m).

Example 24

N-(2-(4-Chlorophenyl)ethyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 2-(4-chlorophenyl)-ethylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.81 (1H, br s), 7.69 (1H, br s), 7.51 (2H, m), 7.37 (2H, d, 8.7), 7.29 (2H, d, 8.7), 3.48-3.35 (4H, m), 3.14-3.06 (4H, m), 2.97-2.93 (2H, m), 2.78 (2H, t, 7.2), 2.00-1.87 (4H, m), 1.73-1.63 (2H, m), 1.53-1.43 (2H, m). Microanalysis found C 45.33 H 7.78 N 12.39. C₁₇H₂₉Cl₃N₄·3H₂O requires C 45.39 H 7.84 N 12.45.

Example 25

N-(2-(4-Chlorophenyl)ethyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 2-(4-chlorophenyl)-ethylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.84 (1H, br s), 7.78 (1H, br s), 7.69 (1H, br s), 7.49 (2H, br s), 7.38-7.29 (4H, m), 3.51-3.37 (4H, m), 3.14-3.03 (4H, m), 2.98-2.90 (2H, m), 2.78 (2H, t, 7.2), 1.99-1.84 (4H, m), 1.72-1.62 (2H, m), 1.48-

1.41 (2H, m), 1.36-1.29 (2H, m). Microanalysis found C 52.33 H 7.91 N 13.38.
C₁₈H₃₁Cl₃N₄-requires C 52.75 H 7.62 N 13.67.

Example 26

5 *N*-(2-(4-Bromophenyl)ethyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with 2-(4-bromophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 11.12 (1H, br s), 8.00 (1H, br s), 7.89 (1H, br s), 7.64 (2H, br s), 7.47 (2H, d, 9), 7.25 (2H, d, 9), 3.48-
10 3.26 (6H, m), 3.15-3.10 (2H, m), 2.99-2.95 (2H, m), 2.77 (2H, t, 7.2), 1.97-1.87 (6H, m). Microanalysis found C 44.77 H 6.59 N 13.29. C₁₆H₂₇BrCl₂N₄ requires C 45.09 H 6.39 N 13.14.

Example 27

15 *N*-(4-Chlorobenzyl)-*N'*-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-guanidine bis-hydrochloride. The product was prepared as in Example 2 with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step a. ¹H NMR (DMSO-*d*₆) 10.84 (1H, br s), 8.28 (1H, br s), 8.05 (1H, br t, 6), 7.69 (2H, br s), 7.46-7.23 (4H, m), 4.42 (2H, d, 6), 3.46-2.90 (5H, m), 2.74-2.73 (3H, br s), 2.14-1.87
20 (6H, m). Microanalysis found C 49.05 H 6.88 N 15.32 C₁₅H₂₅Cl₃N₄ requires C 48.99 H 6.85 N 15.24.

Example 28

N-Adamantan-1-yl-methyl-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

25 The title compound was prepared as in Example 17 with 3-buten-1-ol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.94 (1H, br s), 7.65 (1H, br s), 7.57 (2H, m), 3.53-3.48 (2H, m), 3.29-3.24 (2H, m), 3.17-3.12 (2H, m), 2.99-2.93 (2H, m), 2.83 (2H, d, 5.7), 1.98-1.87 (9H, m), 1.69-1.56 (6H, m), 1.49
30 (6H, br s). Microanalysis found C 52.99 H 9.57 N 12.92. C₁₉H₃₆Cl₂N₄·2H₂O requires C 53.39 H 9.43 N 13.11.

Example 29

N-Adamantan-1-yl-methyl-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.86 (1H, br s), 7.92 (1H, br s), 7.67 (1H, br s), 7.52 (2H, br s), 3.51-3.46 (2H, m), 3.20-3.06 (4H, m), 3.00-2.91 (2H, m), 2.83 (2H, d, 5.7), 2.00-1.84 (7H, m), 1.77-1.50 (16H, m). Microanalysis found C 54.25 H 9.72 N 12.46. C₂₀H₃₈Cl₂N₄·2H₂O requires C 54.41 H 9.59 N 12.69.

Example 30

N-Adamantan-1-yl-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.80 (1H, br s), 7.84 (1H, br s), 7.63 (1H, br s), 7.49 (2H, br s), 3.49-3.44 (2H, m), 3.17-3.90 (6H, m), 2.82 (2H, d, 5.7), 1.94-1.86 (7H, m), 1.73-1.49 (16H, m), 1.40-1.35 (2H, m). Microanalysis found C 54.09 H 9.77 N 12.01. C₂₁H₄₀Cl₂N₄·2.6H₂O requires C 54.09 H 9.77 N 12.01.

15

Example 31

N-Adamantan-1-yl-methyl-*N'*-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as Example 17 with 6-hepten-1-ol replacing 4-penten-1-ol in step a and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.91 (1H, br s), 7.86 (1H, br s), 7.69 (1H, br s), 7.49 (2H, br s), 3.48-3.43 (2H, m), 3.16-3.02 (4H, m), 2.96-2.90 (2H, m), 2.84 (2H, d, 6), 1.98-1.84 (7H, m), 1.68-1.49 (16H, m), 1.32 (4H, br s). Microanalysis found C 56.07 H 9.89 N 11.88. C₂₂H₄₂Cl₂N₄·2H₂O requires C 56.28 H 9.88 N 11.93.

Example 32

N-Adamantan-1-yl-methyl-*N'*-(7-pyrrolidin-1-yl-heptyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 7-octen-1-ol replacing 4-penten-1-ol in step a and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.85 (1H, br s), 7.81 (1H, br s), 7.65 (1H, br s), 7.47 (2H, br s), 3.48-3.43 (2H, m), 3.16-2.89 (6H, m), 2.84 (2H, d, 6), 1.98-1.83 (7H, m), 1.68-1.56 (8H, m), 1.48 (8H, br s), 1.29 (6H, m). Microanalysis found C 58.15 H 10.30 N 11.84. C₂₃H₄₄Cl₂N₄·1.66H₂O requires C 57.86 H 9.99 N 11.73.

30

Example 33

N-(2-Adamantan-1-yl-ethyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-adamantan-1-yl-ethanol

5 replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 10.94 (1H, br s), 7.79 (1H, br s), 7.55 (1H, br s), 7.49 (2H, br s), 3.50-3.49 (2H, m), 3.30-3.24 (2H, m), 3.14-3.11 (4H, m), 2.9-2.94 (2H, m), 1.98-1.86 (9H, m), 1.70-1.58 (6H, m), 1.49-1.39 (6H, m), 1.32-1.27 (2H). Microanalysis found C 56.35 H 9.69 N 13.28. C₂₀H₃₈Cl₂N₄·H₂O requires C 56.73 H 9.52 N 13.23.

10

Example 34

N-(3-Adamantan-1-yl-propyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol

15 replacing 4-methoxybenzyl alcohol in step a. ¹H NMR (DMSO-*d*₆) 10.97 (1H, br s), 7.82 (1H, br s), 7.70 (1H, br s), 7.50 (2H, br s), 3.53-3.46 (2H, m), 3.28-3.24 (2H, m), 3.16-3.07 (4H, m), 3.01-2.91 (2H, m), 1.98-1.86 (9H, m), 1.68-1.56 (6H, m), 1.47-1.43 (8H, m), 1.06-1.01 (2H, m). Microanalysis found C 59.69 H 10.00 N 13.04.

C₂₁H₄₀Cl₂N₄·0.28H₂O requires C 59.41 H 9.63 N 13.20.

20

Example 35

N-(2-Adamantan-1-yl-ethyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a 2-Pent-4-enyl-isoindole-1,3-dione. The potassium derivative of phthalimide

(7.11g, 38.4mmol) and 5-bromo-1-pentene (5.00ml, 42.2mmol) in DMF (100ml) were

25 heated at 70°C for 2h. The reaction mixture was allowed to cool to ambient

temperature and diluted with ethyl acetate (100ml). The organic phase was washed

sequentially twice with water (250ml) and brine (250ml) and was dried over

anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to give

the title compound (6.44g, 78%). ¹H NMR 7.86-7.82 (2H, m), 7.74-7.70 (2H, m),

30 5.87-5.78 (1H, m), 5.10-4.96 (2H, m), 3.71 (2H, t, 7.2), 2.16-2.05 (2H, m), 1.85-1.75 (2H, m).

Step b 4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyraldehyde. The title compound

was prepared as in Example 17 step c with the product from Example 35 step a

replacing the product of Example 17 step b. ¹H NMR 9.78 (1H, t, 1.2), 7.88-7.82 (2H, m), 7.76 (2H, m), 3.77-3.72 (2H, m), 2.57-2.52 (2H, m), 2.05-2.00 (2H, m).

Step c *2-(4-Pyrrolidin-1-yl-butyl)-isoindole-1,3-dione*. The title compound was prepared as in Example 17 step d with the product from Example 35 step b replacing the product of Example 17 step c. ¹H NMR 7.85-7.80 (2H, m), 7.73-7.68 (2H, m), 3.71 (2H, t, 7.2), 2.49-2.44 (6H, m), 1.78-1.68 (6H, m), 1.61-1.51 (2H, m).

Step d *4-Pyrrolidin-1-yl-butylamine*. A solution of the product from step c (4.32g, 15.9mmol) and hydrazine hydrate (3.85ml, 79.4mmol) in ethanol (75ml) was heated at reflux for 1.5h. The resultant white suspension was diluted with further ethanol (50ml) and the solid removed by filtration. The filtrate was evaporated at reduced pressure and the residue was suspended in chloroform (50ml). The solid was removed by filtration and the filtrate evaporated at reduced pressure to afford the title compound (1.91g, 85%). ¹H NMR 2.74-2.69 (2H, m), 2.52-2.42 (6H, m), 1.83-1.75 (4H, m), 1.64-1.46 (6H, m).

Step e *N-(2-Adamantan-1-yl-ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride*. The title compound was prepared as in Example 3 with 2-adamantan-1-yl-ethanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.96 (1H, br s), 7.83 (1H, br s), 7.60 (1H, br s), 7.47 (2H, br s), 3.49-3.44 (2H, m), 3.19-3.04 (6H, m), 2.97-2.95 (2H, m), 1.97-1.87 (7H, m), 1.76-1.48 (16H, m), 1.30-1.25 (2H). Microanalysis found C 57.79 H 9.88 N 12.83. C₂₁H₄₀Cl₂N₄·H₂O requires C 57.65 H 9.68 N 12.81.

Example 36

Step a *N-(3-Adamantan-1-yl-propyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride*

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.98 (1H, br s), 7.85 (1H, br s), 7.73 (1H, br s), 7.49 (2H, br s), 3.47-3.45 (2H, m), 3.17-2.95 (8H, m), 1.96-1.43 (25H, m), 1.06-1.01 (2H, m). Microanalysis found C 58.71 H 10.24 N 12.16. C₂₂H₄₂Cl₂N₄·H₂O requires C 58.52 H 9.82 N 12.41.

Example 37

N-(2-Adamantan-1-yl-ethyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 35 with 6-bromo-1-hexene replacing 5-bromo-1-pentene in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.80 (1H, br s), 7.50 (1H, br s), 7.43 (2H, br s), 3.47-3.43 (4H, m), 3.14-2.94 (6H, m), 1.98-1.86 (7H, m), 1.69-1.25 (20H, m). Microanalysis found C 57.71 H 10.28 N 11.89. C₂₂H₄₂Cl₂N₄·1.4H₂O requires C 57.60 H 9.84 N 12.21.

Example 38

N-(3-Adamantan-1-yl-propyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.84 (1H, br s), 7.72 (1H, br s), 7.64 (1H, br s), 7.43 (2H, br s), 3.47-3.45 (2H, m), 3.14-3.04 (6H, m), 2.96-2.94 (2H, m), 1.97-1.91 (7H, m), 1.69-1.34 (20H, m), 1.06-1.00 (2H, m). Microanalysis found C 59.42 H 10.17 N 12.22. C₂₃H₄₄Cl₂N₄·H₂O requires C 59.34 H 9.96 N 12.03.

Example 39

N-Cyclohexyl-methyl-*N'*-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 3-buten-1-ol replacing 4-penten-1-ol in step a, and cyclohexyl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.82 (1H, br s), 7.71 (1H, br s), 7.50 (2H, m), 3.56-3.48 (2H, m), 3.29-3.23 (2H, m), 3.16-3.11 (2H, m), 3.00-2.93 (4H, m), 1.98-1.83 (6H, m), 1.71-1.67 (5H, m), 1.47-1.46 (1H, m), 1.21-1.08 (3H, m), 0.95-0.84 (2H). Microanalysis found C 48.04 H 9.69 N 14.98. C₁₅H₃₂Cl₂N₄·2H₂O requires C 48.00 H 9.67 N 14.93.

Example 40

N-Cyclohexyl-methyl-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with cyclohexyl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.90

(1H, br s), 7.80 (1H, br s), 7.51 (2H, m), 3.50-3.45 (2H, m), 3.20-3.07 (4H, m), 3.00-2.96 (4H, m), 1.97-1.85 (4H, m), 1.72-1.45 (10H, m), 1.20-1.08 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 48.40 H 9.90 N 13.96. $C_{16}H_{34}Cl_2N_4 \cdot 2.5H_2O$ requires C 48.23 H 9.87 N 14.06.

5

Example 41

N-Cyclohexyl-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and cyclohexyl-methylamine replacing 4-chlorobenzylamine in
10 step b. 1H NMR (DMSO- d_6) 10.9 (1H, br s), 7.78 (1H, br s), 7.72 (1H, br s), 7.45 (2H, m), 3.50-3.44 (2H, m), 3.17-2.90 (8H, m), 1.99-1.83 (4H, m), 1.70-1.63 (7H, m), 1.51-1.31 (5H, m), 1.20-1.06 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 55.57 H 9.88 N 15.25. $C_{17}H_{36}Cl_2N_4$ requires C 55.28 H 10.03 N 14.97.

15 **Example 42**

N-(2-Cyclohexyl-ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-cyclohexyl-ethanol replacing 4-methoxybenzyl alcohol in step a. 1H NMR (DMSO- d_6) 10.92 (1H, br s), 7.78 (1H, br s), 7.64 (1H, br s), 7.49 (2H, br s), 3.50-3.46 (2H, m), 3.28-3.25 (2H, m), 3.14-3.12
20 (4H, m), 2.99-2.96 (2H, m), 1.98-1.86 (6H, m), 1.68-1.65 (5H, m), 1.47-1.09 (6H, m), 0.93-0.86 (2H, m). Microanalysis found C 49.49 H 10.18 N 14.44. $C_{16}H_{34}Cl_2N_4 \cdot 2H_2O$ requires C 49.35 H 9.84 N 14.39.

Example 43

25 *N-(3-Cyclohexyl-propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.*

The title compound was prepared as in Example 3 with 3-cyclohexyl-propanol replacing 4-methoxybenzyl alcohol in step a. 1H NMR (DMSO- d_6) 11.1 (1H, br s), 7.92 (1H, br s), 7.81 (1H, br s), 7.56 (2H, br s), 3.48-3.47 (2H, m), 3.29-3.24 (2H, m), 3.17-3.06 (4H, m), 2.99-2.97 (2H, m), 1.97-1.86 (6H, m), 1.67-1.63 (5H, m), 1.49-1.44
30 (2H, m), 1.19-1.05 (6H, m), 0.89-0.82 (2H, m). Microanalysis found C 53.14 H 10.16 N 14.28. $C_{17}H_{36}Cl_2N_4 \cdot H_2O$ requires C 52.98 H 9.94 N 14.54.

Example 44

N-(1(R)-Cyclohexyl-ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 1-(R)-cyclohexyl-ethylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.80 (1H, br s), 7.58 (1H, d, 9), 7.46 (2H, m), 3.48-3.46 (3H, m), 3.20-3.06 (4H, m), 2.97-2.91 (2H, m), 1.97-1.85 (4H, m), 1.76-1.49 (9H, m), 1.30-0.91 (9H, m). Microanalysis found C 50.49 H 10.14 N 13.66. C₁₇H₃₆Cl₂N₄-2H₂O requires C 50.61 H 9.99 N 13.89.

Example 45

N-(1(*S*)-Cyclohexyl-ethyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 1-(*S*)-cyclohexyl-ethylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.80 (1H, br s), 7.58 (1H, d, 9), 7.46 (2H, m), 3.48-3.46 (3H, m), 3.20-3.06 (4H, m), 2.97-2.91 (2H, m), 1.97-1.85 (4H, m), 1.76-1.49 (9H, m), 1.30-0.91 (9H, m). Microanalysis found C 50.49 H 10.14 N 13.66. C₁₇H₃₆Cl₂N₄-2H₂O requires C 50.61 H 9.99 N 13.89.

Example 46

N-Cycloheptyl-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with cycloheptyl-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.88 (1H, br s), 7.78-7.74 (2H, m), 7.46 (2H, s), 3.50-3.44 (2H, m), 3.17-2.94 (8H, m), 1.99-1.83 (4H, m), 1.70-1.38 (17H, m), 1.19-1.09 (2H, m). Microanalysis found C 47.74 H 10.45 N 12.33. C₁₈H₃₈Cl₂N₄-4H₂O requires C 47.67 H 10.22 N 12.35.

Example 47

N-Benzyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and benzylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.7 (1H, br s), 8.09 (1H, br s), 7.85 (1H, br s), 7.56 (2H, br s), 7.40-7.27 (5H, m), 4.43 (2H, d, 6), 3.47-3.46 (2H, m), 3.17-2.92 (6H, m), 1.97-1.86 (4H, m), 1.66 (2H, m), 1.49-1.46 (2H, m), 1.33-1.30 (2H, m). Microanalysis found C 51.62 H 8.71 N 14.25. C₁₇H₃₀Cl₂N₄-2H₂O requires C 51.38 H 8.62 N 14.10.

Example 48*N*-(2-Methylbenzyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 2-methylbenzylamine replacing 4-chlorobenzylamine in step

- 5 b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 8.02 (2H, br s), 7.64 (2H, br s), 7.20 (4H, m), 4.40 (2H, d, 6), 3.46-3.43 (2H, m), 3.20-3.18 (2H, m), 3.05-2.93 (4H, m), 2.28 (3H, s), 1.96-1.87 (4H, m), 1.68 (2H, m), 1.51-1.48 (2H, m), 1.36-1.30 (2H, m). Microanalysis found C 48.48 H 8.98 N 12.33. C₁₈H₃₂Cl₂N₄·4H₂O requires C 48.32 H 9.01 N 12.52.

10 **Example 49**

N-(1(*S*)-Phenyl-ethyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 1-(*S*)-phenylethylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.8 (1H, br s), 8.35 (1H, br s), 7.90 (1H, br s), 7.58 (2H,

- 15 br s), 7.40-7.24 (5H, m), 4.94-4.86 (1H, m), 3.46-3.43 (2H, m), 3.13-2.91 (6H, m), 1.96-1.86 (4H, m), 1.63 (2H, m), 1.41-1.39 (5H, m), 1.24 (2H, m). Microanalysis found C 52.49 H 8.73 N 13.41. C₁₈H₃₂Cl₂N₄·2H₂O requires C 52.55 H 8.82 N 13.62.

Example 50

20 *N*-Benzyl-*N*-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

- Step a** *N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-benzyl-*N''*-methyl-guanidine. To an ice-cooled solution of *N*-benzylmethylamine (1.94ml, 15.0mmol) in DCM (90ml) was added sequentially triethylamine (6.26ml, 45.0mmol), 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (2.90g, 10.0mmol) and mercury (II) chloride (2.72g, 10.0mmol). The coolant was removed and the resultant suspension was stirred at ambient temperature for 72h. The suspension was filtered through a plug of celite and the filter-cake was washed with further DCM (20ml). The filtrate was washed sequentially with 10% aqueous citric acid (100ml), 10% aqueous potassium carbonate (100ml) and brine (100ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure. The crude residue was purified by flash column chromatography (3:1 hexane ethyl acetate) to afford the title compound (3.02g, 83%). ¹H NMR 10.17 (1H, br s), 7.38-7.27 (5H, m), 4.71 (2H, br s), 2.90 (3H, s), 1.52 (9H, s), 1.50 (9H, s).
- 25
- 30

- Step b** *N,N'*-Bis(*tert*-butoxycarbonyl)-*N*-(5-bromo-pentyl)-*N''*-benzyl-*N'''*-methyl-guanidine. To an ice-cooled solution of the product from step a (1.07g, 2.95mmol) in DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 141mg, 3.58mmol) in a single portion. The coolant was removed and the suspension was
- 5 stirred at ambient temperature for 20 minutes. The suspension was re-cooled in ice and treated in a single portion with 1,5-dibromopentane (1.20ml, 8.81mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The reaction was quenched with water (50ml) and extracted with ethyl acetate (40ml). The aqueous phase was discarded and the organic phase washed twice with
- 10 brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the crude residue purified by flash column chromatography (3:1 hexane ethyl acetate) to afford the title compound (1.24g, 82%).
- Step c** *N,N'*-Bis(*tert*-butoxycarbonyl)-*N''*-benzyl-*N'''*-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine. To an ice-cooled solution of the product from step b (1.24g,
- 15 2.42mmol) in acetonitrile (6ml) was treated with pyrrolidine (0.404ml, 4.84mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure and the crude residue was purified by flash column chromatography (100:10:1 DCM:methanol:ammonia) to afford the title compound (1.14g, 94%).
- 20 **Step d** *N*-Benzyl-*N*-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride. The title compound was prepared as in Example 2 step c with the product from Example 50 step c replacing the product of Example 2 step b. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.84 (1H, br s), 7.75 (2H, br s), 7.42-7.19 (5H, m), 4.66 (2H, s), 3.45-3.41 (2H, m), 3.24-3.22 (2H, m), 3.03-2.93 (7H, m), 1.96-1.89 (4H, m), 1.68 (2H, m),
- 25 1.51-1.49 (2H, m), 1.30-1.28 (2H, m). Microanalysis found C 50.22 H 9.04 N 13.07. C₁₈H₃₂Cl₂N₄·3H₂O requires C 50.34 H 8.92 N 13.05.

Example 51

- N*-(5-Pyrrolidin-1-yl-pentyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamide bis-hydrochloride.
- 30

The title compound was prepared as in Example 50 with tetrahydroisoquinoline replacing *N*-benzylamine in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 8.01 (1H, br s), 7.83 (2H, br s), 7.22-7.15 (4H, m), 4.62 (2H, s), 3.65 (2H, t, 6), 3.46-3.44 (2H, m), 3.25-3.24 (2H, m), 3.06-3.03 (2H, m), 2.92-2.88 (4H, m), 1.96-1.89 (4H, m), 1.70 (2H,

m), 1.56 (2H, m), 1.35 (2H, m). Microanalysis found C 54.14 H 8.66 N 12.99.
C₁₉H₃₂Cl₂N₄·2H₂O requires C 53.92 H 8.57 N 13.24.

Example 52

5 *N,N'*-Bis-(4-Chlorobenzyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a (4-Chlorobenzyl)-carbamic acid tert-butyl ester. To a stirred solution of 4-chlorobenzylamine (9.86g, 69.6mmol) in 1,4-dioxan (100ml) was added dropwise a solution of di-tert-butyl dicarbonate (15.2g, 69.6mmol) in 1,4-dioxan (50ml). The solution was stirred at ambient temperature for 45 minutes and then the solvent was
10 evaporated at reduced pressure. The residue was suspended in hexane (300ml) and the solid recovered by filtration. The solid was washed with further hexane (50ml) and dried *in vacuo* at 50°C to afford the title compound (13.5g, 80%). ¹H NMR 7.31-7.20 (4H, m), 4.80 (1H, br s), 4.27 (2H, d, 5.7), 1.46 (9H, s).

Step b (4-Chlorobenzyl)-pent-4-enyl-carbamic acid tert butyl ester. The title
15 compound was prepared as in Example 35 step a with the product from Example 52 step a replacing the potassium derivative of phthalimide. ¹H NMR 7.31 (2H, d, 7.8), 7.18 (2H, d, 7.8), 5.84-5.71 (1H, m), 5.04-4.95 (2H, m), 4.39 (2H br s), 3.16 (2H, br s), 2.05-1.98 (2H, m), 1.62-1.57 (2H, m), 1.47 (9H, s).

Step c (4-Chlorobenzyl)-pent-4-enyl-amine bis-hydrochloride. The title compound
20 was prepared as in Example 2 step c with the product from Example 52 step b replacing the product of Example 2 step b. ¹H NMR 9.57 (2H, br s), 7.64 (2H, d, 8.4), 7.49 (2H, d, 8.4), 5.83-5.70 (1H, m), 5.07-4.96 (2H, m), 4.10 (2H, s), 2.84-2.79 (2H, m), 2.10-2.03 (2H, m), 1.81-1.71 (2H, m).

Step d N-(4-Chlorobenzyl)-N',N''-bis(tert-butoxycarbonyl)-N-pent-4-enyl-guanidine.
25 The title compound was prepared as in Example 50 step a with the product from Example 52 step c replacing N-benzylmethylaniline.

Step e N-N'-Bis-(4-Chlorobenzyl)-N',N''-bis(tert-butoxycarbonyl)-N-pent-4-enyl-guanidine. The title compound was prepared as in Example 2 step a with the product from Example 52 step d replacing 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-
30 thiopseudourea.

Step f N-N'-Bis-(4-Chlorobenzyl)-N',N''-bis(tert-butoxycarbonyl)-N-(4-oxo-butyl)-guanidine. The title compound was prepared as in Example 17 step c with the product from Example 52 step e replacing the product of Example 17 step b.

Step g *N,N'*-Bis-(4-Chlorobenzyl)-*N',N''*-bis(tert-butoxycarbonyl)-*N*-(4-pyrrolidin-1-yl-butyl)-guanidine. The title compound was prepared as in Example 17 step d with the product from Example 52 step f replacing the product of Example 17 step c.

- Step h** *N,N'*-Bis-(4-Chlorobenzyl)-*N*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride. The title compound was prepared as in Example 2 step c with the product from Example 52 step g replacing the product of Example 2 step b. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 8.66 (1H, br s), 7.93-7.92 (2H, br s), 7.44-7.21 (8H, m), 4.75 (2H, s), 4.51-4.49 (2H, m), 3.44 (4H, br s), 3.06-3.04 (2H, m), 2.90 (2H, m), 1.95-1.86 (4H, m), 1.64 (4H, br s). Microanalysis found C 49.28 H 6.41 N 9.79.
- 10 C₂₃H₃₂Cl₄N₄·3H₂O requires C 49.30 H 6.83 N 10.00.

Example 53

N-(Naphthalen-2-yl-methyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)guanidine bis-hydrochloride.

- The title compound was prepared as in Example 2 with 2-bromomethylnaphthalene replacing 4-chlorobenzyl bromide in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 8.34 (1H, br s), 8.03 (1H, br s), 8.01-7.83 (4H, m), 7.67 (2H, br s), 7.53-7.45 (3H, m), 4.61 (2H, d, 6), 3.45-3.43 (2H, m), 3.21-3.19 (2H, m), 2.99-2.89 (4H, m), 1.94-1.85 (4H, m), 1.65 (2H, m), 1.49-1.47 (2H, m), 1.32-1.29 (2H, m). Microanalysis found C 56.11 H 8.06 N 12.67. C₂₁H₃₂Cl₂N₄·2H₂O requires C 56.37 H 8.11 N 12.52.
- 20

Example 54

N-Biphenyl-4-yl-methyl-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

- The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 8.31 (1H, br s), 8.07 (1H, br s), 7.68-7.64 (6H, m), 7.48-7.33 (5H, m), 4.50 (2H, d, 6), 3.45-3.43 (2H, m), 3.23-3.21 (2H, m), 3.11-3.07 (2H, m), 2.92 (2H, m), 1.97-1.85 (4H, m), 1.70 (2H, m), 1.56-1.54 (2H, m). Microanalysis found C 57.72 H 7.89 N 12.24. C₂₂H₃₂Cl₂N₄·1.88H₂O requires C 57.78 H 7.88 N 12.25.
- 30

Example 55

N-Biphenyl-4-yl-methyl-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 8.29 (1H, br s), 8.01 (1H, br s), 7.68-7.65 (6H, m), 7.48-7.33 (5H, m), 4.49 (2H, d, 6), 3.51-3.41 (2H, m), 3.22-3.16 (2H, m), 3.05-2.98 (2H, m), 2.92-2.87 (2H, m), 1.94-1.83 (4H, m), 1.72-1.62 (2H, m), 1.52-1.45 (2H, m), 1.33-1.31 (2H, m). Microanalysis found C 58.13 H 8.13 N 11.88. C₂₃H₃₄Cl₂N₄·2H₂O requires C 58.34 H 8.09 N 11.83.

Example 56

10 *N*-(4-Cyclohexylbenzyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.
The title compound was prepared as in Example 3 with (4-cyclohexylphenyl)-methanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 8.21 (1H, br s), 8.06 (1H, br s), 7.65 (2H, br s), 7.25 (2H, d, 6), 7.18
15 (2H, d, 6), 4.39 (2H, d, 6), 3.45-3.44 (2H, m), 3.21-3.19 (2H, m), 3.11-3.07 (2H, m), 2.94 (2H, m), 1.96-1.23 (19H, m). Microanalysis found C 56.75 H 9.23 N 11.88. C₂₂H₃₈Cl₂N₄·2H₂O requires C 56.76 H 9.09 N 12.04.

Example 57

20 *N*-(4-Cyclohexylbenzyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride
The title compound was prepared as in Example 3 with (4-cyclohexylphenyl)-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 8.13 (1H, br s), 7.93 (1H, br s), 7.59 (2H, br s), 7.24-7.18 (4H, m),
25 4.38 (2H, d, 6), 3.50-3.43 (2H, m), 3.20-3.13 (2H, m), 3.08-2.92 (4H, m), 2.49 (1H, m), 1.99-1.63 (11H, m), 1.51-1.23 (9H, m). Microanalysis found C 56.38 H 9.33 N 11.48. C₂₃H₄₀Cl₂N₄·2.5H₂O requires C 56.55 H 9.28 N 11.47.

Example 58

30 *N*-(5-Pyrrolidin-1-yl-pentyl)-*N'*-(tetrahydro-pyran-2-yl-methyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and tetrahydro-pyran-2-yl-methylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.74 (1H, br s),

7.52 (1H, br s), 7.46 (2H, br s), 3.90-3.86 (1H, m), 3.47-3.03 (12H, m), 1.96-1.33 (16H, m). Microanalysis found C 48.40 H 9.61 N 13.88. $C_{16}H_{34}Cl_2N_4O \cdot 1.5H_2O$ requires C 48.48 H 9.41 N 14.13.

5 Example 59

N-Adamantan-1-yl-methyl-N'-(2-(2-pyrrolidin-1-yl-ethoxy)-ethyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 2-allyloxy-ethanol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-

10 chlorobenzylamine in step b. 1H NMR (DMSO- d_6) 10.4 (1H, br s), 8.06 (1H, br s), 7.75 (1H, br s), 7.65 (2H, br s), 3.75-3.72 (2H, m), 3.55-3.53 (4H, m), 3.41-3.34 (4H, m), 3.07-3.04 (2H, m), 2.88 (2H, d, 5.7), 1.94 (7H, br s), 1.68-1.51 (12H, m).

Microanalysis found C 57.07 H 8.96 N 13.18. $C_{20}H_{38}Cl_2N_4O$ requires C 57.00 H 9.09 N 13.29.

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Example 60

N-Adamantan-1-yl-methyl-N'-(5-piperidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in

20 step b, and piperidine replacing pyrrolidine in step d. 1H NMR (DMSO- d_6) 10.44 (1H, br s), 7.89 (1H, br s), 7.68 (1H, br s), 7.51 (2H, br s), 3.32 (3H, br s), 3.15 (2H, q, 6.3), 2.94 (2H, m), 2.83 (4H, m), 1.93 (3H, br s), 1.83-1.45 (20H, m), 1.34 (3H, m).

Microanalysis found C 52.28 H 9.90 N 11.03. $C_{22}H_{42}Cl_2N_4 \cdot 4H_2O$ requires C 52.27 H 9.97 N 11.08.

25

Example 61

N-Adamantan-1-yl-methyl-N'-(5-azepan-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in

30 step b, and hexamethyleneimine replacing pyrrolidine in step d. 1H NMR (DMSO- d_6) 10.54 (1H, br s), 7.88 (1H, br s), 7.67 (1H, br s), 7.50 (2H, br s), 3.29 (2H, br s), 3.15 (2H, q, 6.4), 3.02 (4H, m), 2.83 (2H, d, 6), 1.94 (3H, br s), 1.80-1.40 (24H, m), 1.34 (2H, m). Microanalysis found C 53.01 H 10.17 N 10.40. $C_{23}H_{44}Cl_2N_4 \cdot 4H_2O$ requires C 53.17 H 10.09 N 10.78.

Example 62

N-Adamantan-1-yl-methyl-N'-(5-azocan-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and heptamethyleneimine replacing pyrrolidine in step d. ¹H NMR (DMSO-*d*₆) 10.50 (1H, br s), 7.88 (1H, br s), 7.66 (1H, br s), 7.50 (2H, br s), 3.30 (2H, br s), 3.16-2.98 (6H, m), 2.83 (2H, d, 6), 1.94 (3H, br s), 1.83-1.40 (26H, m), 1.34 (2H, m). Microanalysis found C 54.00 H 10.32 N 10.43. C₂₄H₄₆Cl₂N₄·4H₂O requires C 54.02 H 10.20 N 10.50.

Example 63

N-Adamantan-1-yl-methyl-N'-(5-(4-methyl-piperazin-1-yl)-pentyl)-guanidine tris-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and 1-methyl-piperazine replacing pyrrolidine in step d. ¹H NMR (DMSO-*d*₆) 12.0 (2H, br s), 7.86 (1H, br s), 7.67 (1H, br s), 7.50 (2H, br s), 3.75-3.25 (8H, m), 3.14 (4H, m), 2.84-2.80 (5H, m), 1.94 (3H, br s), 1.73-1.40 (16H, m), 1.35 (2H, m). Microanalysis found C 50.70 H 9.52 N 13.49. C₂₂H₄₄Cl₃N₅·2H₂O requires C 50.72 H 9.29 N 13.44.

Example 64

N-(4-Chlorobenzyl)-N'-methyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.

Step a 1-(4-Chlorobenzyl)-3-methyl-thiourea. To an ice-cooled aqueous solution of methylamine (40%w/w, 10ml) was added a solution of 4-chlorobenzylisocyanate (1.84g, 10.0mmol) in 1,4-dioxan (10ml). The coolant was removed and the reaction was stirred at ambient temperature for 1h. The reaction mixture was partitioned between ethyl acetate (40ml) and water (40ml). The aqueous phase was discarded and the organic phase washed with brine (40ml), and was dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound (2.02g, 94%). ¹H NMR 7.91 (1H, br m), 7.52 (1H, br m), 7.39-7.28 (4H, m), 4.62 (2H, d, 3.9), 2.82 (3H, bd, 2.4).

Step b *1-(4-Chlorobenzyl)-2,3-dimethyl-isothioureia iodide*. A solution of the product of step a (2.00g, 9.27mmol) and iodomethane (0.866ml, 13.9mmol) in acetone (20ml) was heated at reflux for 2h. The reaction mixture was cooled in ice to give rise to a white precipitate. The solid was isolated by filtration and the solid was washed with cold acetone to afford the title compound (2.92g, 88%). ¹H NMR (DMSO-*d*₆) 9.80-8.80 (2H, br m), 7.46 (2H, d, 8.7), 7.35 (2H, d, 8.7), 4.58 (2H, s), 3.00-2.95 (3H, br s), 2.70-2.59 (3H, br s).

Step c *N-(4-Chlorobenzyl)-N'-methyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine*. A solution of the product from step b (358mg, 1.00mmol) and 3-pyrrolidin-1-yl-propylamine (0.19ml) in ethanol (4ml) was stirred at ambient temperature for 16h followed by heating at reflux for 1h. The solvent was removed at reduced pressure and the residue was partitioned between DCM (20ml) and aqueous ammonia (880, 20ml). The aqueous phase was extracted with further DCM (10ml) and then discarded. The combined organic phases were washed twice with water (20ml) and once with brine (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated to afford the title compound (225mg, 73%). ¹H NMR 7.40-7.29 (4H, m), 4.60 (2H, s), 3.42-3.47 (2H, m), 2.97 (3H, s), 2.50-2.44 (6H, m), 1.83-1.63 (6H, m).

20 **Example 65**

N-Butyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine.

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and n-butylamine replacing 4-chlorobenzylamine in step b. ¹H NMR 3.15 (4H, br m), 2.43-2.34 (6H, br m), 1.74 (4H, br s), 1.56-1.42 (6H, m), 1.35-1.28 (4H, m), 0.86 (3H, t, 7.2). The title compound was converted to the bis-maleic acid salt and lyophilised from 1,4-dioxan and water.

Example 66

N-(3-Methyl-butyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

30 The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and *iso*-amylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.79 (1H, br s), 7.69 (1H, br s), 7.47 (2H, br s), 3.50-3.43 (2H, m), 3.16-2.90 (8H, m), 1.99-1.85 (4H, m), 1.73-1.32 (9H, m), 0.88 (6H, d, 6.6).

Example 67

N-(2-Methyl-butyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-

- 5 penten-1-ol in step a, and 2-methyl-butylamine replacing 4-chlorobenzylamine in step b. ¹H NMR (DMSO-d₆) 10.9 (1H, br s), 7.85 (1H, br s), 7.75 (1H, br s), 7.50 (2H, br s), 3.50-3.44 (2H, m), 3.15-2.90 (8H, m), 1.99-1.83 (4H, m), 1.73-1.34 (8H, m), 1.56-1.06 (1H, m), 0.87-0.82 (6H, m).

10 **Example 68**

N-(4-Chlorobenzyl)-*N*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a (4-Chlorobenzyl)-(4-oxo-butyl)-carbamic acid tert-butyl ester. The title compound was prepared as in Example 17 step c with the product from Example 52 step b replacing the product of Example 17 step b. ¹H NMR 9.75 (1H, m), 7.29 (2H, d, 8.1), 7.15 (2H, d, 8.1), 4.39 (2H, s), 3.21 (2H, br s), 2.43 (2H, br s), 1.85-1.80 (2H, m), 1.47 (9H, s).

- Step b** (4-Chlorobenzyl)-(4-pyrrolidin-1-yl-butyl)-carbamic acid tert-butyl ester. The title compound was prepared as in Example 17 step d with the product from Example 68 step a replacing the product of Example 17 step c. ¹H NMR 7.30-7.27 (2H, m), 7.17-7.15 (2H, m), 4.38 (2H, br s), 3.21 (2H, br m), 2.52 (6H, br s), 1.81 (4H, br s), 1.46 (13H, m).

- Step c** (4-Chlorobenzyl)-(4-pyrrolidin-1-yl-butyl)-amine bis-hydrochloride. The title compound was prepared as in Example 2 step c with the product from Example 68 step b replacing the product of Example 2 step b. ¹H NMR (DMSO-d₆) 11.0 (1H, bs), 9.50 (2H, br s), 7.61 (2H, d, 8.4), 7.48 (2H, d, 8.4), 4.11 (2H, s), 3.44 (2H, br s), 3.08-2.87 (6H, m), 1.92 (4H, br s), 1.73 (4H, br s).

- Step d** *N,N'*-Bis(tert-butyloxycarbonyl)-*N''*-(4-chlorobenzyl)-*N''*-(4-pyrrolidin-1-yl-butyl)-guanidine. The title compound was prepared as in Example 50 step a with the product from Example 68 step c replacing *N*-benzylmethylamine. ¹H NMR 9.97 (1H, br s), 7.32-7.22 (4H, m), 4.67 (2H, s), 3.34-3.29 (2H, m), 2.51-2.36 (6H, m), 1.76-1.70 (4H, m), 1.50-1.41 (22H, m).

Step e *N*-(4-Chlorobenzyl)-*N*-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride. The title compound was prepared as in Example 2 step c with the product from Example 68 step d replacing the product of Example 2 step b. ¹H NMR (DMSO-d₆)

11.0 (1H, br s), 7.73 (4H, br s), 7.46 (2H, d, 6), 7.27 (2H, d, 6), 4.64 (2H, s), 3.47-3.28 (4H, m), 3.05-2.89 (4H, m), 1.95-1.86 (4H, m), 1.62-1.58 (4H, m). Microanalysis found C 45.72 H 7.49 N 13.40. C₁₆H₂₇Cl₃N₄·2H₂O requires C 46.00 H 7.48 N 13.41.

5 Example 69

N-(4-Chlorobenzyl)-*N*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

Step a (5-Bromo-pentyl)-(4-chlorobenzyl)-carbamic acid tert-butyl ester. To an ice-cooled stirred solution of the product from Example 52 step a (725mg, 3.00mmol) in DMF (9ml) was added, in a single portion, sodium hydride (60% dispersion in mineral oil, 144mg, 3.60mmol). The coolant was removed and the suspension was stirred at ambient temperature for 30 minutes. The suspension was cooled in ice and 1,5-dibromopentane (1.23ml, 9.03mmol) was added in three portions. The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The reaction was quenched with water (40ml) and then extracted with ethyl acetate (40ml). The aqueous phase was discarded and the organic phase washed twice with brine (40ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (5:1 hexane:ethyl acetate) to afford the title product.

Step b (4-Chlorobenzyl)-(5-pyrrolidin-1-yl-pentyl)-amine bis-hydrochloride. To a stirred solution of the product from step a in acetonitrile (4ml) was added pyrrolidine (1.27ml, 15.2mmol). The solution was stirred at ambient temperature for 18h. The reaction mixture was diluted with ethyl acetate (50ml) and washed sequentially with water (50ml) and brine (50ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue treated with hydrogen chloride in 1,4-dioxan (10ml). The solution was stirred at ambient temperature for 1h and the solvent removed at reduced pressure to afford the title compound (655mg, 62%). ¹H NMR (DMSO-*d*₆) 12.1 (1H, br s), 10.8 (1H, br s), 9.47 (1H, br s), 7.64 (2H, d, 9), 7.53 (2H, d, 9), 4.10 (2H, s), 3.46-3.45 (2H, m), 3.06-2.85 (6H, m), 1.97-1.64 (8H, m), 1.37-1.35 (2H, m).

Step c *N,N'*-Bis(tert-butyloxycarbonyl)-*N''*-(4-chlorobenzyl)-*N''*-(5-pyrrolidin-1-yl-pentyl)-guanidine. The title compound was prepared as in Example 50 step a with the product from Example 69 step b replacing *N*-benzylmethylamine. ¹H NMR 9.95 (1H, br s), 7.32-7.22 (4H, m), 4.67 (2H, s), 3.32-3.27 (2H, m), 2.48-2.36 (6H, m), 1.78 (4H, br s), 1.60-1.42 (22H, m), 1.30-1.22 (2H, m).

Step d *N*-(4-Chlorobenzyl)-*N*-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 step c with the product from Example 69 step c replacing the product of Example 2 step b. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.67-7.61 (4H, br m), 7.46 (2H, d, 6), 7.27 (2H, d, 6), 4.62 (2H, s), 3.46-3.44 (2H, m), 3.27-3.24 (2H, m), 3.03-2.90 (4H, m), 1.96-1.86 (4H, m), 1.65-1.52 (4H, m), 1.30-1.27 (2H, m). Microanalysis found C 47.21 H 7.66 N 13.26. C₁₇H₂₉Cl₃N₄-2H₂O requires C 47.28 H 7.70 N 12.97.

Example 7010 *N*-(4-Chlorobenzyl)-*N*-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,6-dibromohexane replacing 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.68 (4H, br s), 7.47 (2H, d, 9), 7.27 (2H, d, 9), 4.62 (2H, s), 3.48-3.38 (2H, m), 3.29-3.24 (2H, m), 3.05-2.88 (4H, m), 1.98-1.80 (4H, m), 1.66-1.58 (2H, m), 1.50 (2H, br s), 1.27-1.26 (4H, m). Microanalysis found C 49.47 H 7.72 N 12.83. C₁₈H₃₁Cl₃N₄-1.5H₂O requires C 49.49 H 7.85 N 12.83.

Example 71*N*-(4-Chlorobenzyl)-*N*-(7-pyrrolidin-1-yl-heptyl)-guanidine bis-hydrochloride

20 The title compound was prepared as in Example 69 with 1,7-dibromoheptane replacing 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.72 (4H, br s), 7.46 (2H, d, 9), 7.27 (2H, d, 9), 4.62 (2H, s), 3.48-3.41 (2H, m), 3.26 (2H, t, 7.5), 3.05-2.86 (4H, m), 1.98-1.82 (4H, m), 1.64 (2H, m), 1.48 (2H, br m), 1.24 (6H, br s). Microanalysis found C 49.70 H 7.98 N 12.24. C₁₉H₃₃Cl₃N₄-2H₂O requires C 49.62 H 8.11 N 12.18.

Example 72*N*-(4-Chlorobenzyl)-*N*-(6-piperidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,6-dibromohexane replacing 1,5-dibromopentane in step a, and piperidine replacing pyrrolidine in step b. ¹H NMR (DMSO-*d*₆) 10.6 (1H, br s), 7.71 (4H, br s), 7.46-7.43 (2H, m), 7.27-7.25 (2H, m), 4.62 (2H, s), 3.38-3.24 (4H, m), 2.94-2.73 (4H, m), 1.89-1.24 (14H, m). Microanalysis found C 49.47 H 7.90 N 12.11. C₁₉H₃₃Cl₃N₄-2H₂O requires C 49.62 H 58.11 N 12.18.

Example 73

N-Benzyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

Step a *Benzyl-carbamic acid tert-butyl ester*. The title compound was prepared as in

- 5 Example 52 step a with benzylamine replacing 4-chlorobenzylamine. ¹H NMR 7.36-7.28 (5H, m), 4.83 (1H, br s), 4.33 (2H, d, 5.7), 1.47 (9H, s).

- Step b** *N-Benzyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride*. The title compound was prepared as in Example 69 with the product from step a and 1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.72 (4H, br s), 7.41-7.22 (5H, m), 4.62 (2H, s), 3.47-3.41 (2H, m), 3.29-3.24 (2H, m), 3.05-2.88 (4H, m), 1.98-1.79 (4H, m), 1.66-1.58 (2H, m), 1.49 (2H, br s), 1.26-1.25 (4H, m).

Microanalysis found C 50.49 H 8.99 N 13.22. C₁₈H₃₂Cl₂N₄·3H₂O requires C 50.34 H 8.92 N 13.05.

15

Example 74

N-(4-Bromobenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

- Step a** *(4-Bromobenzyl)-carbamic acid tert-butyl ester*. To a stirred suspension of 4-bromo-benzylamine hydrochloride (968mg, 4.35mmol) and triethylamine (0.666ml, 20 4.79mmol) in chloroform (15ml) was added di-*tert*-butyldicarbonate (949mg, 4.35mmol). The resulting solution was stirred at ambient temperature for 2h and then diluted with DCM (40ml). The organic solution was washed sequentially with 10% aqueous citric acid (40ml) and brine (40ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure to afford 25 the title compound (1.23g, 99%). ¹H NMR 7.48-7.43 (2H, m), 7.18 (2H, d, 8.4), 4.84 (1H, br s), 4.27 (2H, d, 5.7), 1.46 (9H, s).

- Step b** *N-(4-Bromobenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride*. The title compound was prepared as in Example 69 with the product from step a and 1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.71 (4H, br s), 7.59 (2H, d, 9), 7.21 (2H, d, 9), 4.61 (2H, s), 3.46-3.24 (4H, m), 3.03-2.90 (4H, m), 1.95-1.84 (4H, m), 1.64 (2H, br s), 1.49 (2H, br s), 1.25 (4H, br s). Microanalysis found C 42.41 H 7.31 N 11.05. C₁₈H₃₁BrCl₂N₄·3H₂O requires C 42.53 H 7.34 N 11.02.
- 30

Example 75

N-(1-(S)-Phenyl-ethyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

Step a *(1-(S)-Phenyl-ethyl)-carbamic acid tert-butyl ester*. The title compound was prepared as in Example 52 step a with 1-(S)-phenyl-ethylamine replacing 4-

5 chlorobenzylamine. ¹H NMR 7.36-7.28 (5H, m), 4.78 (2H, br s), 1.47-1.43 (12H, m).

Step b *N-(1-(S)-Phenyl-ethyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-*

hydrochloride. The title compound was prepared as in Example 69 with the product

from step a replacing the product of Example 52 step a in step a.. ¹H NMR (DMSO-

*d*₆) 10.9 (1H, br s), 7.71 (4H, br s), 7.44-7.31 (5H, m), 5.34 (1H, q, 6), 3.45-3.36 (2H,

10 m), 3.16-2.84 (6H, m), 1.97-1.82 (4H, m), 1.62-1.05 (9H, m). Microanalysis found C

53.71 H 8.86 N 13.66. C₁₈H₃₂Cl₂N₄·1.5H₂O requires C 53.73 H 8.77 N 13.92.

Example 76

N-(2-Methylbenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

15 **Step a** *(2-Methylbenzyl)-carbamic acid tert-butyl ester*. The title compound was

prepared as in Example 52 step a with 2-methylbenzylamine replacing 4-

chlorobenzylamine. ¹H NMR 7.27-7.17 (4H, m), 4.60 (1H, br s), 4.33 (2H, d, 5.4),

2.34 (3H, s), 1.47 (9H, s).

Step b *N-(2-Methylbenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride*.

20 The title compound was prepared as in Example 69 with the product from step a and

1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-

dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.64 (4H, br s), 7.21-

7.20 (3H, m), 6.95-6.94 (1H, m), 4.56 (2H, s), 3.45-3.36 (2H, m), 3.25-3.22 (2H, m),

3.03-2.91 (4H, m), 2.24 (3H, s), 1.95-1.85 (4H, m), 1.64-1.53 (4H, m), 1.27-1.26 (4H,

25 m). Microanalysis found C 51.30 H 9.32 N 12.32. C₁₉H₃₄Cl₂N₄·3H₂O requires C

51.46 H 9.09 N 12.63.

Example 77

N-Adamantan-1-yl-methyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

30 **Step a** *Adamantane-1-carboxylic acid (6-hydroxy-hexyl)-amide*. To an ice-cooled

solution of 6-amino-1-hexanol (3.52g, 30.0mmol) and triethylamine (4.17ml,

30.0mmol) in DCM (40ml) was added dropwise a solution of 1-adamantanecarbonyl

chloride (3.97g, 20.0mmol). The coolant was removed and the resulting suspension

was stirred at ambient temperature for 4h. The reaction mixture was washed

sequentially with 10% aqueous citric acid (100ml), aqueous 2M sodium hydroxide (100ml) and brine (100ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure to afford the title compound (3.58g, 64%). ¹H NMR 5.59 (1H, br s), 3.63 (2H, t, 6.3), 3.28-3.21 (2H, m), 2.04 (3H, s), 1.85 (6H, br s), 1.77-1.72 (7H, m), 1.57-1.32 (8H, m).

Step b *Toluene-4-sulfonic acid 6-((adamantane-1-carbonyl)-amino)-hexyl ester*. To an ice-cooled solution of the product from step a (3.58g, 12.8mmol), triethylamine (3.13ml, 22.5mmol) and 4-dimethylaminopyridine (catalytic amount) in DCM (25ml) was added, in a single portion, *p*-toluenesulfonyl chloride (4.28g, 22.4mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 3h. The reaction mixture was washed sequentially with 10% aqueous citric acid (30ml), 10% aqueous potassium carbonate (30ml) and brine (30ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure to afford the title compound.

Step c *Adamantane-1-carboxylic acid (6-pyrrolidin-1-yl-hexyl)-amide*. To an ice-cooled solution of the product from step b in acetonitrile (25ml) was added pyrrolidine (6.41ml, 76.8mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 20h. The mixture was partitioned between ethyl acetate (100ml) and water (100ml). The aqueous phase was discarded and the organic phase extracted with aqueous 2M hydrochloric acid (100ml). The organic phase was discarded and the aqueous phase was washed with further ethyl acetate (50ml). The pH of the aqueous phase was adjusted to pH 11 and then extracted twice with chloroform (100ml). The combined organic phases were washed with brine (100ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound (4.34g, 100%). ¹H NMR 5.54 (1H, br s), 3.26-3.20 (2H, m), 2.50-2.40 (6H, m), 2.05 (3H, s), 1.85-1.73 (14H, m), 1.52-1.50 (4H, m), 1.36-1.33 (4H, m).

Step d *Adamantan-1-yl-methyl-(6-pyrrolidin-1-yl-hexyl)-amine bis-hydrochloride*. To a solution of the product from step c (2.00g, 6.02mmol) in THF (20ml) was added a solution of lithium aluminium hydride (1.0M in THF, 12.0ml, 12.0mmol). The reaction mixture was heated at reflux for 23h and allowed to cool. The reaction mixture was quenched sequentially with water (0.46ml), aqueous 2M sodium hydroxide (0.46ml) and water (1.37ml). Ethyl acetate (30ml) and anhydrous magnesium sulfate added and the suspension filtered through a plug of celite. The

filter-cake was washed sequentially with ethyl acetate (70ml) and chloroform (100ml). The filtrate was evaporated at reduced pressure and the residue treated with hydrogen chloride in 1,4-dioxan (10ml). The solvent was evaporated at reduced pressure and the residue suspended in ether (50ml). The solid was isolated by vacuum filtration and washed with further ether. The solid was dried *in vacuo* to afford the title compound.

Step e *N,N'*-Bis(tert-butyloxycarbonyl)-*N''*-(adamantan-1-yl-methyl)-*N''*-(6-pyrrolidin-1-yl-hexyl)-guanidine. The title compound was prepared as in Example 50 step a with the product from Example 77 step d replacing N-benzylmethylamine. ¹H NMR 9.30 (1H, br s), 3.43 (2H, br s), 3.16 (2H, br s), 2.51-2.40 (6H, m), 1.79 (4H, br s), 1.70-1.49 (34H, m), 1.31-1.30 (4H, m).

Step f *N*-Adamantan-1-yl-methyl-*N*-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride. The title compound was prepared as in Example 2 step c with the product from Example 77 step e replacing the product of Example 2 step b. ¹H NMR (DMSO-*d*₆) 11.0 (1H, br s), 7.85 (4H, br s), 3.49-3.42 (2H, m), 3.36-3.28 (2H, m), 3.06-2.89 (6H, m), 1.98-1.83 (7H, m), 1.68-1.47 (16H, m), 1.30-1.23 (4H, m).

Microanalysis found C 56.11 H 9.83 N 11.73. C₂₂H₄₂Cl₂N₄·2H₂O requires C 56.28 H 9.88 N 11.93.

Example 78

N-(2-Adamantan-1-yl-ethyl)-*N*-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride. The title compound was prepared as in Example 77 with adamantan-1-yl-acetyl chloride replacing adamantylcarbonyl chloride in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.43 (4H, br s), 3.45-3.42 (2H, m), 3.28-3.19 (4H, m), 3.07-2.92 (4H, m), 1.95-1.85 (7H, m), 1.68-1.48 (16H, m), 1.29-1.28 (6H, m). Microanalysis found C 52.93 H 10.02 N 10.83. C₂₃H₄₄Cl₂N₄·4H₂O requires C 53.17 H 10.09 N 10.78.

Example 79

N-(4-Chlorobenzyl)-*N*-(8-pyrrolidin-1-yl-octyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,8-dibromooctane replacing 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 10.9 (1H, br s), 7.62 (4H, br s), 7.47-7.43 (2H, m), 7.26-7.24 (2H, m), 4.60 (2H, s), 3.46-3.44 (2H, m), 3.28-3.23 (2H, m), 3.04-2.92 (4H, m), 1.95-1.85 (4H, m), 1.64 (2H, br s), 1.48 (2H, br s), 1.23 (8H, br s). Microanalysis found C 51.66 H 8.33 N 11.92. C₂₀H₃₅Cl₃N₄·1.55H₂O requires C 51.57 H 8.24 N 12.03.

Example 80*N-(4-Chlorobenzyl)-N-(9-pyrrolidin-1-yl-nonyl)-guanidine bis-hydrochloride*

The title compound was prepared as in Example 69 with 1,9-dibromononane replacing

- 5 1,5-dibromopentane in step a. ¹H NMR (DMSO-*d*₆) 11.1 (1H, br s), 7.70 (4H, br s), 7.46 (2H, d, 9), 7.27 (2H, d, 9), 4.61 (2H, s), 3.46-3.41 (2H, m), 3.28-3.23 (2H, m), 3.04-2.92 (4H, m), 1.95-1.85 (4H, m), 1.64 (2H, br s), 1.47 (2H, br s), 1.21 (10H, br s). Microanalysis found C 51.79 H 8.48 N 11.37. C₂₁H₃₇Cl₃N₄·2H₂O requires C 51.69 H 8.47 N 11.48.

10

Example 81*N-(2-Pyrrolidin-1-yl-ethyl)-2-naphthalenesulfonamide*

To an ice-cooled solution of 2-pyrrolidin-1-yl-ethylamine (1.00g, 8.76mmol) and triethylamine (1.22ml, 8.76mmol) in DCM (20ml) was added portionwise 2-

- 15 naphthalenesulfonyl chloride (1.98g, 8.73mmol). The coolant was removed and the resultant solution was stirred at ambient temperature for 16h. The organic phase was washed sequentially twice with water (20ml) and brine (20ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to obtain the title compound as a white solid (1.81g, 68%). ¹H NMR 8.45 (1H, d, 1.5), 7.99-7.83 (4H, m), 7.66-7.61 (2H, m), 5.80-5.20 (1H, br s), 3.06-3.02 (2H, m), 2.53 (2H, m), 12.36-2.32 (4H, m), 1.74-1.65 (4H, m). Microanalysis found C 62.96 H 6.74 N 9.11. C₁₆H₂₀N₂O₂S requires C 63.13 H 6.62 N 9.20.

20

Example 82

- 25 *N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfonamide*

The title compound was prepared as in Example 81 with 3-pyrrolidin-1-yl-propylamine replacing 2-pyrrolidin-1-yl-ethylamine.

¹H NMR 8.43 (1H, s), 7.99-7.59 (7H, m), 3.11 (2H, t, 5.7), 2.54-2.49 (6H, m), 1.81 (4H, m), 1.68-1.63 (2H, m).

Microanalysis found C 63.85 H 7.04 N 8.76. C₁₇H₂₂N₂O₂S requires C 64.12 H 6.96 N

- 30 8.80.

Example 83*N-(4-Pyrrolidin-1-yl-butyl)-2-naphthalenesulfonamide*

The title compound was prepared as in Example 81 with 4-pyrrolidin-1-yl-butylamine replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.41 (1H, s), 7.90 (4H, m), 7.60 (2H, m), 2.96 (2H, t), 2.69 (4H, m), 2.59 (2H, t), 1.92 (4H, m), 1.61 (4H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.49, H 6.90, N 7.14. C₁₈H₂₅ClN₂O₂S requires C 57.26, H 6.93, N 7.42.

Example 84

N-(2-Piperidin-1-yl-ethyl)-2-naphthalenesulfonamide

- 10 The title compound was prepared as in Example 81 with 2-piperidin-1-yl-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.45 (1H, s), 7.93 (3H, m), 7.83 (1H, m), 7.64 (2H, m), 2.99 (2H, t), 2.31 (2H, t), 2.14 (4H, m), 1.44 (6H, m). Found C 63.88, H 7.03, N 8.87. C₁₇H₂₂N₂O₂S requires C 64.12, H 6.96, N 8.79.

15 Example 85

N-(4-(4-Methyl-piperazin-1-yl)-butyl)-2-naphthalenesulfonamide

- The title compound was prepared as in Example 81 with 4-(4-methyl-piperazin-1-yl)-butylamine replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.43 (1H, s), 7.86 (4H, m), 7.63 (2H, m), 3.00 (2H, t), 2.54 (8H, m), 2.32 (6H, m), 1.54 (4H, m). The bis-hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated to afford the title compound as a white solid. Found C 52.14, H 6.92, N 9.58. C₁₉H₂₉Cl₂N₃O₂S requires C 52.53, H 6.73, N 9.67.

Example 86

N-(2-Pyrrolidin-1-yl-ethyl)-N-methyl-2-naphthalenesulfonamide.

- To an ice-cooled solution of 2-naphthalenesulfonyl chloride (2.27g, 10.0mmol) and triethylamine (2.00ml, 14.4mmol) in DCM (30ml) was added methyl-(2-pyrrolidin-1-yl-ethyl)-amine¹ (1.28g, 10.0mmol). The coolant was removed and the resultant solution stirred at ambient temperature for 1.5h. The organic phase was washed sequentially twice with water (30ml), then brine (30ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (100:10:1 DCM:methanol:ammonia). The purified material was treated with aqueous hydrochloric acid (1M, 20ml) and the resultant solid was removed by filtration and dried *in vacuo* to obtain the title

compound as a white solid (909mg, 26%). ¹H NMR (DMSO-*d*₆) 10.52 (1H, br s), 8.51 (1H, s), 8.22-8.07 (3H, m), 7.84-7.68 (3H, m), 3.59-3.37 (6H, m), 3.09-3.01 (2H, m), 2.77 (3H, s), 2.01-1.87 (4H, m). Microanalysis found C 57.28 H 6.74 N 7.83. C₁₇H₂₃ClN₂O₂S requires C 57.53 H 6.53 N 7.89.

5

Example 87

N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide.

Step a Naphthalene-2-sulfinic acid methyl ester. To an ice-cooled suspension of 2-naphthalenethiol (2.16g, 18.7mmol) and potassium carbonate (5.68g, 41.1mmol) in methanol (60ml) was added N-bromosuccinimide (7.32g, 41.1mmol). The coolant was removed after 10 minutes and the reaction mixture stirred at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (70ml) and washed sequentially with water (100ml), twice with saturated aqueous sodium hydrogen carbonate (70ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound (2.34g, 83%). ¹H NMR 8.28 (1H, s), 8.01-7.92 (3H, m), 7.72-7.60 (3H, m), 3.51 (3H, s).

Step b N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide. To a cooled (-30°C) solution of 3-pyrrolidin-1-yl-propylamine (641mg, 5.00mmol) in THF (10ml) was added a solution of lithium diisopropylamide (1.5M, 3.30ml, 4.95mmol). The solution was stirred at this temperature for 20 minutes and then added dropwise to a cooled (-78°C) solution of the product of step a (1.03g, 5.00mmol) in THF (10ml). The reaction was stirred at this temperature for 3h and then allowed to warm to ambient temperature and stirred at ambient temperature for 16h. The reaction was quenched with saturated aqueous ammonium chloride (70ml) and then extracted thrice with ethyl acetate (70ml). The combined organic layers were extracted with aqueous hydrochloric acid (1M, 100ml) and the acidic phase washed with ethyl acetate (70ml). The pH of the acidic phase was adjusted (pH11) with ammonia (880) and extracted thrice with DCM (70ml). The combined DCM extracts were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography to obtain the title compound (54mg, 3%). The title compound was converted to the corresponding hydrochloride salt with hydrogen chloride in 1,4-dioxan. ¹H NMR (DMSO-*d*₆) 9.79 (1H, s), 8.43-

8.06 (4H, m), 7.83-7.67 (4H, m), 3.45-3.44 (2H, m), 3.10-3.07 (2H, m), 2.90-2.81 (4H, m), 1.95-1.74 (6H, m). Microanalysis found C 57.43 H 6.75 N 7.73. $C_{17}H_{23}ClN_2OS \cdot 0.5HCl$ requires C 57.17 H 6.63 N 7.84.

5 Example 88

1-[4-(Naphthalene-2-sulfonyl)-butyl]-pyrrolidine

Step a 4-(2-Naphthalenesulfonyl)-butanoic acid ethyl ester. To a stirred ice-cooled solution of 2-naphthalenethiol (3.20g, 20.0mmol) in DMF (40ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 880mg, 22.0mmol). The suspension was stirred at this temperature for 15 minutes and then treated with a solution of ethyl 4-bromobutyrate (3.15ml, 22.0mmol) in DMF (20ml). The coolant was removed and the reaction mixture was stirred at ambient temperature for 16h. The reaction mixture was partitioned between ethyl acetate (200ml) and water (200ml), and the aqueous phase discarded. The organic phase was washed twice with brine (200ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (5:1 hexane:ethyl acetate) to afford the title compound (4.56%, 83%). 1H NMR 7.78-7.74 (4H, m), 7.48-7.42 (3H, m), 4.15 (2H, q, 7.2), 3.08 (2H, t, 7.2), 2.50 (2H, t, 7.2), 2.07-1.97 (2H, m), 1.25 (3H, t, 7.2).

Step b 4-(2-Naphthalenesulfonyl)-butyric acid methyl ester. To a solution of the product of step a (1.04g, 3.80mmol) in DCM (10ml) was added in a single portion *meta*-chloroperoxybenzoic acid (3.27g, 11.37mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The reaction was diluted with DCM (70ml) and washed sequentially with saturated aqueous sodium hydrogen carbonate (100ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound (1.02g, 88%). 1H NMR 8.50 (1H, s), 8.04-7.86 (4H, m), 7.70-7.42 (2H, m), 4.09 (2H, q, 7.2), 3.30-3.25 (2H, m), 2.46 (2H, t, 7.2), 2.12-2.05 (2H, m), 1.22 (3H, t, 7.2).

Step c 4-(2-Naphthalenesulfonyl)-butan-1-ol. To a cooled ($-78^{\circ}C$) solution of the product of step b (1.00g, 3.27mmol) in THF (10ml) was added dropwise a solution of lithium aluminium hydride (1M, THF, 3.50ml, 3.50mmol) and the mixture was stirred at this temperature for 3h. The reaction mixture was treated sequentially with water

(0.14ml), aqueous sodium hydroxide (2M, 0.14ml) and water (0.42ml) and allowed to warm to ambient temperature. Sodium sulfate was added and the resultant suspension filtered through a pad of celite and the filter-cake washed with further ethyl acetate (150ml). The filtrate was evaporated at reduced pressure and the residue purified by
5 flash column chromatography (3:1 ethyl acetate:hexane) to afford the title compound (524mg, 61%). ¹H NMR 8.50 (1H, s), 8.04-7.86 (4H, m), 7.72-7.63 (2H, m), 3.66-3.62 (2H, m), 3.27-3.21 (2H, m), 1.91-1.83 (2H, m), 1.71-1.65 (2H, m), 1.56 (1H, br s).

Step d 4-(2-Naphthalenesulfonyl)-butyraldehyde. To a solution of the product of step
10 c (524mg, 1.98mmol) and triethylamine (0.829ml, 5.96mmol) in DMSO (10ml) was added a solution of sulfur trioxide-pyridine (948mg, 5.96mmol) in DMSO (10ml) and the reaction mixture stirred at ambient temperature for 15 minutes. The reaction mixture was poured into ice-water (150ml) and then extracted thrice with ethyl acetate (60ml). The combined organic phases were washed with aqueous citric acid (70ml)
15 and brine (70ml), then dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (2:1 ethyl acetate:hexane) to afford the title compound (457mg, 88%). ¹H NMR 9.75 (1H, s), 8.50 (1H, s), 8.05-7.65 (6H, m), 3.26-3.22 (2H, m), 2.71 (2H, t, 6.9), 2.15-2.04 (2H, m).

Step e 1-[4-(Naphthalene-2-sulfonyl)-butyl]-pyrrolidine. The title compound was prepared as in Example 17 step d with the product from Example 88 step d replacing the product of Example 17 step c. ¹H NMR 8.50 (1H, m), 8.04-7.86 (4H, m), 7.72-7.64 (2H, m), 3.24-3.19 (2H, m), 2.42-2.37 (6H, m), 1.86-1.56 (8H, m). Microanalysis found C 68.22 H 7.45 N 4.38. C₁₈H₂₃NO₂S requires C 68.10 H 7.30 N 4.41.
25

Example 89

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.42 (1H, s), 7.85 (4H, m), 7.62 (2H, m), 3.05 (3H, m), 2.26 (1H, m), 2.25 (3H, s), 2.10 (1H, m), 1.76-1.48 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.21, H 6.79, N 7.96. C₁₇H₂₃Cl N₂O₂S requires C 57.53, H 6.53, N 7.89.
30

Example 90

N-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide

Step a *N*-(tert-Butoxycarbonyl)-2-piperidin-2-yl-ethanol. The title compound was prepared as in Example 52 step a with 2-piperidin-2-yl-ethanol replacing 4-

5 chlorobenzylamine. ¹H NMR 4.40 (1H, br m), 3.97-3.93 (1H, br m), 3.63-3.56 (1H, br m), 3.36 (1H, br m), 2.72-2.63 (1H, m), 1.98-1.89 (1H, m), 1.75-1.27 (16H, m).

Step b 2-(2-Amino-ethyl)-piperidine-1-carboxylic acid *t*-butyl ester. To an ice-cooled solution of the product of step a (5.00g, 21.8mmol), triphenylphosphine (7.41g, 28.3mmol) and phthalimide (4.16g, 28.3mmol) in THF (50ml) was added dropwise

10 diethylazodicarboxylate (4.45ml, 28.3mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). A solution of this material in ethanol (100ml) was treated with hydrazine hydrate (5.30ml) and the resultant reaction mixture was heated at reflux for
15 1h. The resultant solid was removed by filtration and the filter-cake washed with further ethanol (50ml). The filtrate was evaporated at reduced pressure and the residue was suspended in chloroform (50ml) and the solid residue was removed by filtration. The filtrate was evaporated at reduced pressure to afford the title compound as an oil (2.58g, 52%). ¹H NMR 4.36 (1H, br s), 3.95 (1H, bd, 13.5), 2.77-2.60 (3H, m), 1.99-
20 1.93 (1H, m), 1.70-1.38 (18H, m).

Step c *N*-(2-(1-(tert-Butoxycarbonyl) piperidin-2-yl)-ethyl)-naphthalenesulfonamide.

The title compound was prepared as in Example 81 with the product from Example 90 step b replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.42 (1H, m), 7.97-7.82 (4H, m), 7.64-7.59 (2H, m), 4.28-4.24 (1H, m), 3.88-3.84 (1H, m), 3.19 (1H, m), 2.60-2.53
25 (2H, m), 1.91-1.87 (1H, m), 1.64-1.28 (16H, m).

Step d *N*-(2-(Piperidin-2-yl)-ethyl)-naphthalenesulfonamide. To a solution of the product of step c (3.29g, 7.89mmol) in CHCl₃ (8ml) was added trifluoroacetic acid (16ml) and the reaction mixture was stirred at ambient temperature for 20h. The excess trifluoroacetic acid was removed at reduced pressure and the residue
30 partitioned between aqueous 10% potassium carbonate (50ml) and CHCl₃ (50ml). The CHCl₃ layer was removed and the aqueous phase was extracted with further CHCl₃ (50ml). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to afford

the title compound (2.42g, 97%). ¹H NMR (CHCl₃) 8.43 (1H, d, 1.5), 7.98-7.86 (4H, m), 7.76-7.60 (2H, m), 3.20-3.01 (5H, m), 2.60-2.55 (2H, m), 1.60-1.19 (8H, m).

Step e *N*-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide. To a stirred solution of the product of step d (2.42g, 7.63mmol) and aqueous formaldehyde (37%,

- 5 3.3ml) in acetonitrile (25ml) was added portionwise sodium cyanoborohydride (788mg, 11.4mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The pH was adjusted to 6 with acetic acid and the resultant solution stirred at ambient temperature for 30 minutes. The mixture was evaporated at reduced pressure and the residue treated with methanol (50ml) and ammonia solution (880,
- 10 50ml). The aqueous phase was extracted twice with DCM (50ml) and the combined organic phases were dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (338mg, 13%) as an oil. The oil was treated with hydrogen chloride in 1,4-dioxan and the solvent removed *in*
- 15 *vacuo*. The residue was suspended in diethyl ether and the solid removed by filtration, to obtain the title compound as the hydrochloride salt. ¹H NMR (DMSO-*d*₆) 10.46-10.23 (1H, br s), 8.45-7.64 (8H, m), 3.01 (1H, m), 3.03-2.80 (4H, m), 2.64-2.56 (3H, m), 2.06-1.34 (8H, m). Microanalysis found C 57.43 H 7.08 N 7.27. C₁₈H₂₅ClN₂O₂S-0.5H₂O requires C 57.21 H 6.93 N 7.41.
- 20

Example 91

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide

Step a *2S*-(Methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

- To a solution of N-tert-butoxycarbonyl-L-proline (10.76 g, 50 mmol), N,N-
- 25 diisopropylethylamine (9.6 ml, 55 mmol), N,O-dimethylhydroxylamine hydrochloride (5.36 g, 55 mmol) and 1-hydroxybenzotriazole (6.75g, 50 mmol) in DCM (150 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (9.5 g, 50 mmol) at 0°C. The solution was stirred at ambient temperature for 16h, washed with water (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), 1N
- 30 hydrochloric acid (100 ml), and water again (100 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to afford the product as a colourless oil (11.1 g, 86%). ¹H NMR 4.70 and 4.60 (1H, 2xm), 3.76 and 3.69 (3H, 2xs), 3.60-3.30 (2H, m), 2.10-1.75 (4H, m), 1.43 and 1.39 (9H, 2xs).

Step b *2S-Formyl-pyrrolidine-1-carboxylic acid tert-butyl ester*. To a suspension of lithium aluminium hydride (2.12 g, 56.0 mmol) in THF (80 ml) was added dropwise a solution of the product from step a (11.1 g, 43 mmol) in THF (80 ml) at 0°C. The temperature was allowed to rise to ambient temperature and the stirring was continued for 1h. The reaction mixture was cooled to 0°C and 2M aqueous sodium hydroxide (11 ml) was slowly added. The mixture was stirred at ambient temperature for 30 mins, the precipitate was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in ethyl acetate (50 ml) and the solution was successively washed with aqueous 1M hydrochloric acid (30 ml), water (30 ml) and brine (30 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated to afford the product as a colourless oil (6.3 g, 74%). ¹H NMR 9.51 and 9.42 (1H, 2xs), 4.10 and 4.00 (1H, 2xm), 3.45 (2H, m), 1.93 (4H, m), 1.43 and 1.40 (9H, 2xs).

Step c *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-acrylic acid ethyl ester*. The product of step b (6.3 g, 31.6 mmol) and (carbethoxymethylene)triphenylphosphorane (11.0 g, 31.6 mmol) were refluxed in THF (50 ml) for 2h. The solvent was evaporated and the residue was triturated with hexane:ethyl acetate 1:1 (60 ml). The precipitate was filtered, the filtrate was evaporated. The residue was purified by flash column chromatography (hexane:ethyl acetate 80:20) to afford colourless oil (8.2 g, 97%). ¹H NMR 6.80 (1H, bd), 5.80 (1H, d), 4.50 and 4.55 (1H, 2xbr s), 4.15 (2H, m), 3.41 (2H, m), 2.00 (1H, m), 1.77 (3H, m), 1.40 (9H, s), 1.24 (3H, t).

Step d *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propionic acid ethyl ester*. A round bottom flask containing the product of step c (8.1 g, 30.2 mmol), 10% palladium-on-charcoal (0.80 g) and THF:methanol 1:1 (150 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred for 2h under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated to afford the title compound as a colourless oil (7.3g, 89%). ¹H NMR 4.10 (2H, m), 3.79 (1H, br s), 3.29 (2H, m), 2.29 (2H, m), 1.90-1.61 (6H, m), 1.43 (9H, s), 1.23 (3H, t).

Step e *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propan-1-ol*. The title compound was prepared as in Example 88 step c with the product from Example 91 step d replacing the product of Example 88 step b. ¹H NMR (DMSO-*d*₆) 4.34 (1H, t), 3.62 (1H, m), 3.38 (2H, m), 3.22 (2H, m), 1.85-1.23 (17H, m).

Step f *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-propylamine*. The title compound was prepared as in Example 90 step b with the product from Example 91 step e

replacing the product of Example 90 step a. ¹H NMR (DMSO-*d*₆) 3.61 (1H, br s), 3.36 (2H, br s), 3.20 (2H, m), 2.49 (2H, m), 1.82-1.16 (17H, m).

Step g *N*-(3-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2*S*-yl)-propyl)-2-naphthalenesulfonamide The title compound was prepared as in Example 81 with the

5 product from Example 91 step f replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.44 (1H, s), 7.92 (4H, m), 7.60 (2H, m), 5.70 and 4.50 (1H, 2xbr s), 3.72 (1H, br s), 3.25 (2H, m), 3.04 (2H, m), 1.87- 1.24 (17H, m).

Step h *N*-(3-(Pyrrolidin-2*S*-yl)-propyl)-2-naphthalenesulfonamide The title compound was prepared as in Example 90 step d with the product from Example 91 step g
10 replacing the product of Example 90 step c. ¹H NMR (DMSO-*d*₆) 8.41(1H, s), 8.11 (2H, m), 8.03 (1H, d), 7.80 (1H, m), 7.67 (2H, m), 6.00 (1H, br s), 2.92-2.75 (5H, m), 1.75 (1H, m), 1.60 (2H, m), 1.39 (4H, m), 1.15 (1H, m).

Step i *N*-(3-(1-Methyl-pyrrolidin-2*S*-yl)-propyl)-2-naphthalenesulfonamide. The title compound was prepared as in Example 90 step e with the product from Example 91
15 step h replacing the product of Example 90 step d. ¹H NMR 8.42 (1H, s), 7.86 (4H, m), 7.63 (4H, m), 3.20 (1H, m), 3.06 (1H, m), 2.83 (1H, m), 2.30 (5H, m), 1.83-1.53 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 55.59, H 7.06, N 7.23. C₁₈H₂₅ Cl N₂O₂S-1.1 mol of H₂O requires C 55.61, H 7.05, N
20 7.21.

Example 92

N-(3-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide.

Step a *N*-(3-Pyridin-3-yl-propyl)-phthalimide. To a stirred ice-cooled solution of 3-
25 pyridinepropanol (1.29ml, 10.0mmol), triphenylphosphine (3.41g, 13.0mmol) and phthalimide (1.91g, 13.0mmol) in THF (20ml) was added in three portions diethylazodicarboxylate (2.23ml, 13.0mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 20h. The reaction mixture was diluted with ethyl acetate (50ml) and extracted twice with aqueous hydrochloric acid
30 (60ml). The acidic phases were combined and treated with ammonia (880) until pH 11 was achieved and then extracted twice with DCM (100ml). The combined organics were washed with brine (100ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to obtain the title compound (2.67g,

100%). ¹H NMR 8.47-8.41 (2H, m), 7.86-7.46 (5H, m), 7.26-7.20 (1H, m), 3.77 (2H, t, 7.2), 2.70 (2H, t, 7.8), 2.10-2.00 (2H, m).

Step b *N*-(3-(1-Methyl-pyridin-3-yl)-propyl)-phthalimide iodide. To a solution of the product of step a (1.33g, 5.00mmol) in acetone (5ml) was added iodomethane (0.467ml, 7.50mmol) and the resultant solution heated at reflux for 4h. The resultant suspension was filtered and the recovered solid washed with ether (50ml) and the title compound (1.50g, 74%) was dried *in vacuo*. ¹H NMR (DMSO-d₆) 8.93 (1H, s), 8.82-8.80 (1H, d, 6), 8.48-8.46 (1H, m), 8.06-8.00 (1H, m), 7.89-7.82 (4H, m), 4.29 (3H, s), 3.65 (2H, t, 6.6), 2.84 (2H, t, 8.1), 2.07-1.93 (2H, m).

10 **Step c** *N*-(3-(1-Methyl-piperidin-3-yl)-propyl)-phthalimide To a cooled (-78°C) suspension of the product of step b (1.49g, 3.65mmol) in methanol (36ml) was added portionwise sodium borohydride (270mg, 7.30mmol) and the resultant suspension stirred at this temperature for 20 minutes. The suspension was allowed to warm to 0°C and the reaction stirred for a further 30 minutes. The suspension was treated with
15 aqueous 2M hydrochloric acid (3.6ml) and the stirring was continued for a further 1h. The reaction mixture was treated with sufficient aqueous 2M sodium hydroxide to pH 11 and water (100ml) was added. The aqueous phase was extracted thrice with DCM (100ml) and the combined organic extracts were dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was dissolved in
20 methanol (10ml) and treated with palladium on charcoal (150mg). The resultant suspension was stirred under a hydrogen atmosphere (*via* balloon) for 16h. The suspension was filtered through a pad of celite and the filter-cake was washed with methanol (100ml). The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to
25 obtain the title compound (437mg, 42%). ¹H NMR 7.87-7.82 (2H, m), 7.74-7.69 (2H, m), 3.72-3.65 (2H, m), 2.89-2.82 (2H, m), 2.28 (3H, s), 1.89-0.84 (11H, m).

Step d *N*-(3-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide. To a stirred solution of the product of step c (437mg, 1.53mmol) in ethanol (10ml) was added hydrazine hydrate (0.37ml) and the reaction heated at reflux for 1.5h. The
30 resultant suspension was filtered, the filter-cake was washed with further ethanol (20ml) and the filtrate was evaporated. The residue was suspended in DCM (20ml) and the solid was removed by filtration. The filtrate was evaporated at reduced pressure and the residue was dissolved in DCM (5ml). The solution was treated sequentially, with ice-cooling, with triethylamine (0.290ml, 2.08mmol) and 2-

naphthalenesulfonyl chloride (217mg, 1.39mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 2h. The reaction was diluted with DCM (20ml), washed with water (20ml) and brine (20ml), and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was
5 purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to afford the title compound (240mg, 45%). ¹H NMR 8.44 (1H, d, 1.2), 7.99-7.59 (6H, m), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.24 (3H, s), 1.87-1.84 (3H, m), 1.64-1.46 (5H, m), 1.21-1.13 (2H, m), 0.75 (1H, m). Microanalysis found C 64.32 H 7.75 N 7.59. C₁₉H₂₆N₂O₂S·0.5H₂O requires C 64.19 H 7.76 N 7.88.

10

Example 93

N-(3-(1-Methyl-piperidin-4-yl)-propyl)-2-naphthalenesulfonamide.

The title compound was prepared as in Example 92 with 4-pyridinepropanol replacing 3-pyridinepropanol. ¹H NMR 8.44 (1H, d, 1.8), 7.99-7.82 (4H, m), 7.66-7.62 (2H, m),
15 4.46 (1H, br m), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.23 (3H, s), 1.85-1.42 (6H, m), 1.21-1.11 (5H, m). Microanalysis found C 66.06 H 7.58 N 8.05. C₁₉H₂₆N₂O₂S requires C 65.86 H 7.56 N 8.09.

Example 94

20 *N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-1-naphthalenesulfonamide.*

The title compound was prepared as in Example 81 with 1-naphthalenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ¹H NMR 8.67 (1H, d), 8.25 (1H, m), 8.06 (1H, d), 7.95 (1H, d), 7.57 (3H, m), 3.07 (1H, m), 2.90 (2H, m), 2.27
25 (4H, m), 2.00 (1H, m), 1.81 (1H, m), 1.55 (4H, m), 1.41 (2H, m). Found C 63.73, H 6.95, N 9.01. C₁₇H₂₂N₂O₂S requires C 64.12, H 6.96, N 8.80.

Example 95

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-toluenesulfonamide.

30 The title compound was prepared as in Example 81 with 4-toluenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. The hydrochloride salt was prepared by treatment with hydrogen chloride in 1,4-dioxan. ¹H NMR (DMSO-*d*₆) 7.62 (2H, d, 8.1), 7.47 (1H, t, 5.1), 7.37 (2H, d, 8.1), 2.86-2.70 (3H, m), 2.37 (3H, s),

2.09 (3H, s), 1.98-1.93 (2H, m), 1.76-1.49 (4H, m), 1.29-1.16 (2H, m). Microanalysis found C 52.52 H 7.30 N 8.53. $C_{14}H_{23}ClN_2O_2S$ requires C 52.73 H 7.27 N 8.79.

Example 96

5 *N*-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-chlorophenylsulfonamide.

The title compound was prepared as in Example 81 with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. The hydrochloride salt was prepared by treatment with hydrogen chloride in 1,4-dioxan. 1H NMR (DMSO- d_6) 8-7 (1H, br s), 7.82-7.77 (2H, m), 7.50-7.46 (2H, m), 3.10-3.01 (3H, m), 2.39 (1H, m), 2.28 (3H, s), 2.15-2.12 (1H, m), 1.82-1.42 (6H, m). Microanalysis found C 51.65 H 6.44 N 8.99. $C_{13}H_{19}ClN_2O_2S$ requires C 51.56 H 6.32 N 9.25.

Example 97

15 *N*-(2-(1-Methyl-pyrrolidin-2*S*-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide.

Step a 2*S*-Hydroxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester. The title compound was prepared as in Example 52 step a with (S)-(+)-pyrrolidinemethanol replacing 4-chlorobenzylamine. 1H NMR 3.94 (1H, m), 3.61 (2H, m), 3.45 (1H, m), 3.30 (1H, m), 2.01 (1H, m), 1.79 (2H, m), 1.58 (1H, m), 1.52 (1H, s), 1.47 (9H, s).

20 **Step b** 2*S*-Tosyloxymethyl-pyrrolidine-1-carboxylic acid tert-butyl ester. To a solution of the product of step a (4.0 g, 20.0 mmol) and triethylamine (3.3 ml, 24.0 mmol) in DCM (100 ml) was added p-toluenesulfonyl chloride (3.8 g, 20.0 mmol) and 4-dimethylaminopyridine (0.2 g) at 0°C. The solution was stirred at ambient temperature for 5h, then it was washed successively with water (50 ml), saturated aqueous sodium
25 hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate 70:30) to afford the title compound (4.3 g, 61 %). 1H NMR 7.77 (2H, d), 7.34 (2H, d), 4.10 (1H, m), 3.90 (2H, m), 3.29 (2H, m), 2.44 (3H, s), 1.92-1.80 (4H, m), 1.37 (9H, s).

30 **Step c** 2*S*-Cyanomethyl-pyrrolidine-1-carboxylic acid tert-butyl ester. The product of step b (4.3 g, 12.1 mmol) and potassium cyanide (1.6 g, 24.2 mmol) were heated together in dimethyl sulfoxide at 110°C for 3h. The reaction mixture was cooled to ambient temperature and poured into water (200 ml). The product was extracted with ethyl acetate (3x50 ml), the combined organic extracts were washed with brine, dried

over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane:ethyl acetate 70:30) to afford the the title compound as a colourless oil (1.46 g, 57.5%). ¹H NMR 4.00 (1H, br s), 3.41 (2H, m), 2.74 (2H, m), 2.16 (1H, m), 1.92 (3H, m), 1.47 (9H, s).

Step d *2S-(2-Aminoethyl)-pyrrolidine-1-carboxylic acid tert-butyl ester*. The product of step c (1.45 g, 6.9 mmol) was suspended in methanol saturated with ammonia (50 ml), Raney-Nickel (ca. 1.0 g) and hydrogen hexachloroplatinate (IV) hydrate (80 mg dissolved in 1 ml of water) were added. The mixture was stirred in a Parr bottle under H₂ pressure (about 40 psi) for 24 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude material was purified by flash chromatography (DCM:methanol:amonia (880) 90:10:1) to afford the title compound (1.18g, 80%). ¹H NMR 3.90 (1H, m), 3.30 (2H, m), 2.71 (2H, t), 1.87-1.45 (17H, m).

Step e *N-(2-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl-ethyl)-(4-chlorophenyl)-methanesulfonamide*. To a solution the product of step d (0.27g, 1.26mmol) and triethylamine (0.23ml, 1.62mmol) in DCM (15 ml), cooled under an atmosphere of argon to -78°C, was added dropwise a solution of (4-chlorophenyl)-methanesulfonyl chloride² (0.34g, 1.5mmol) in DCM (5 ml). The resultant solution was stirred for 18h, allowing to warm to ambient temperature. The solution was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The material was purified by flash column chromatography (DCM:ethyl acetate 90:10) afforded the product (0.29g, 57%). ¹H NMR 7.34 (4H, s), 6.15 (1H, br s), 4.20 (2H, s), 3.96 (1H, m), 3.28 (2H, m), 3.02 (2H, m), 2.80 (1H, m), 1.95-1.45 (6H, m), 1.45 (9H, s).

Step f *N-(2-(1-Methyl-pyrrolidin-2S-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide*.

The product of step e (0.29 g, 0.72 mmol) was dissolved in trifluoroacetic acid (3 ml) and the solution was stirred for 1h. The trifluoroacetic acid was evaporated *in vacuo*, the residue was dissolved in DCM (20 ml) and the organic solution was washed with 10% aqueous potassium carbonate (20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated to afford colourless foam. The foam was dissolved in 1,2-dichloroethane (5 ml) and cooled to 0°C, aqueous formaldehyde (37%, 0.1 ml, 1.4 mmol), followed by sodium triacetoxyborohydride (0.26 g, 1.2 mmol) were added and the mixture was stirred for 2h. Saturated sodium hydrogen carbonate solution was added (20 ml) and the product was extracted with DCM (20ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the

residue was purified by flash column chromatography (DCM:methanol:ammonia (880) 90:10:1) to afford the title compound (0.15g, 67%). ¹H NMR 7.36 (4H, s), 4.19 (2H, s), 3.20 (1H, m), 3.04 (2H, m), 2.50 (1H, m), 2.31 (3H, s), 2.19 (1H, m), 1.86-1.50 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.22, H 6.60, N 8.04. C₁₄H₂₂ Cl₂N₂O₂S requires C 47.59, H 6.28, N 7.93.

Example 98

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-sulfonamide

- 10 The title compound was prepared as in Example 91 with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride in step g. ¹H NMR 7.79 (2H, d), 7.45 (2H, m), 3.12 (1H, m), 3.00 (1H, m), 2.76 (1H, m), 2.24 (3H, s), 2.20 (2H, m), 1.80-1.37 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.76, H 6.35, N 8.11.
- 15 C₁₄H₂₂ Cl₂N₂O₂S requires C 47.59, H 6.28, N 7.93.

Example 99

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-methanesulfonamide

- The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f replacing the product of Example 97 step d in step e. ¹H NMR 7.36 (4H, s), 4.18 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.20 (5H, m), 1.73-1.45 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.64, H 6.67, N 7.28.
- 20 C₁₅H₂₄Cl₂N₂O₂S-0.6 H₂O requires C 47.58, H 6.72, N 7.40.

25

Example 100

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-phenyl-methanesulfonamide

- The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and phenyl-methanesulfonyl chloride replacing respectively
- 30 the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ¹H NMR 7.40 (5H, m), 4.22 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.19 (3H, s), 2.16 (2H, m), 1.71-1.35 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.24, H 7.70, N 8.07. C₁₅H₂₅ClN₂O₂S-1.0H₂O requires C 51.31, H 7.76, N 7.98.

Example 101

N-(3-(1-Methyl-pyrrolidin-2*S*-yl)-propyl)-(4-bromophenyl)-methanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and (4-bromophenyl)-methanesulfonyl chloride² replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ¹H NMR 7.50 (2H, m), 7.27 (2H, m), 4.16 (2H, s), 3.03 (2H, m), 2.88 (1H, m), 2.24 (5H, m), 1.75-1.54 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

10 Found C 43.55, H 5.90, N 6.57. C₁₅H₂₄BrClN₂O₂S requires C 43.75, H 5.87, N 6.80.

Example 102

N-(3-(1-Methyl-pyrrolidin-2*S*-yl)-propyl)-2-(4-chlorophenyl)-ethanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and 2-(4-chlorophenyl)-ethanesulfonyl chloride² replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ¹H NMR 7.29 (2H, m), 7.16 (2H, m), 3.21 (2H, m), 3.09 (4H, m), 2.97 (1H, m), 2.32 (3H, s), 2.23 (2H, m), 1.77-1.41 (8H, m). Found C 55.46, H 7.44, N 8.09. C₁₆H₂₅ClN₂O₂S requires C 55.72, H 7.31, N 8.12.

20

Example 103

N-(3-(1-Methyl-pyrrolidin-2*S*-yl)-propyl)-3-(4-chlorophenyl)-propanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and 2-(4-chlorophenyl)-propanesulfonyl chloride² replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ¹H NMR 7.31 (2H, m), 7.16 (2H, d), 3.14 (2H, m), 3.00 (3H, m), 2.78 (2H, t), 2.35 (3H, s), 2.28 (2H, m), 2.15 (2H, m), 1.78-1.47 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.39, H 7.22, N 7.00. C₁₇H₂₈Cl₂N₂O₂S requires

25

30 C 51.64, H 7.14, N 7.08.

Example 104

N-(4-(1-Methyl-pyrrolidin-2*S*-yl)-butyl)-(4-chlorophenyl)-methanesulfonamide

The title compound was prepared as in Example 97, steps b-f, with the product from Example 91 step e replacing 2S-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester as the substrate in step b. ¹H NMR 7.36 (4H, m), 4.30 (1H, br s), 4.21 (2H, s), 3.09 (1H, m), 3.00 (2H, t), 2.32 (3H, s), 2.19-1.26 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.20, H 6.93, N 7.31. C₁₆H₂₆ Cl₂N₂O₂S requires C 50.39, H 6.87, N 7.35.

Example 105

10 *N*-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamide

Step a 5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentanoic acid ethyl ester. A

solution of triethyl 4-phosphonocrotonate (3.6ml, 16.3mmol) in THF (20ml) was added dropwise to a slurry of sodium hydride (60% dispersion in mineral oil, 0.72g, 18.0mmol) in THF (20ml) at 0°C under an atmosphere of argon. The mixture was

15 allowed to warm to ambient temperature, stirred for 20 mins, then cooled to -20°C and a solution of the product from Example 91 step b in THF (30 ml) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 2h, then it was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic phase was washed with brine, dried over anhydrous magnesium sulfate and the solvent was

20 evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane:ethyl acetate 80:20). A round bottom flask containing the purified material (1.9 g), 10% palladium-on-charcoal (0.2 g) and THF:methanol 1:1 (30 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was

25 removed by filtration and the filtrate evaporated to afford the title compound (1.85 g, 46%). ¹H NMR 4.12 (2H, q), 3.73 (1H, br s), 3.3 (2H, m), 2.30 (2H, t), 1.91-1.60 (8H, m), 1.46 (9H, s), 1.30 (2H, m), 1.25 (3H, t).

Step b 5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentan-1-ol. The title compound was prepared as in Example 88 step c with the product of Example 105 step a

30 replacing the product of Example 88 step b.

Step c 5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentylamine. The title compound was prepared as in Example 90 step b with the product of Example 105 step b replacing the product of Example 90 step a.

Step d *N*-(5-(1-(tert-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamide. The title compound was prepared as in Example 97 step e with the product of Example 105 step c replacing the product of Example 97 step d.

- Step e** *N*-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamide. The title compound was prepared as in Example 97 step f with the product from Example 105 step d replacing the product of Example 97 step e. ¹H NMR 7.33 (4H, m), 4.50 (1H, br s), 4.19 (2H, s), 3.06 (1H, m), 2.97 (2H, t), 2.29 (3H, s), 2.14 (1H, m), 1.96 (2H, m), 1.66 (3H, m), 1.45 (3H, m), 1.25 (5H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.26, H 7.20, N 6.89. C₁₇H₂₈ Cl₂N₂O₂S requires C 51.64, H 7.14, N 7.09.

Example 106

N-(3-Pyrrolidin-1-yl-propyl)-(4-chlorophenyl)-methanesulfonamide

- The title compound was prepared as in Example 97 step e with 3-pyrrolidin-1-yl-propylamine replacing the product of Example 97 step d. ¹H NMR 7.36 (4H, s), 4.19 (2H, s), 3.10 (2H, t), 2.60 (2H, t), 2.47 (4H, br s), 1.68 (6H, m). Found C 52.72, H 6.86, N 8.66%; C₁₄H₂₁ClN₂O₂S requires C 53.07, H 6.68, N 8.84%.

Example 107

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

- Step a** *N*-tert-Butoxycarbonyl-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide. To an ice-cooled solution of chlorosulfonyl isocyanate (0.64ml, 7.4mmol) in DCM (15 ml) was added dropwise a solution of dry *tert*-butanol (1.0 ml, 10.8 mmol) in DCM (10 ml). The solution was allowed to warm to ambient temperature, stirred for 10 min and added dropwise to an ice cooled solution of the product from Example 91 step f (1.3 g, 5.7 mmol) and triethylamine (1.2ml, 8.6mmol) in DCM (20ml). The mixture was stirred for 18h, allowed to warm to ambient temperature. The solution was washed with water (20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Purification by flash column chromatography (DCM:ethyl acetate 90:10) of the residue afforded the title product (1.67g, 72%). ¹H NMR 7.63 (1H, s), 5.50 and 5.30 (1H, 2xbr s), 3.80 (1H, br s), 3.30 (2H, m), 3.09 (2H, br s), 1.92-1.39 (26H, m).

Step b *N*-(*tert*-Butoxycarbonyl)-*N*-(4-Chlorobenzyl)-*N'*-(3-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide. To an ice-cooled solution of the product of step a (1.6g, 3.93mmol) and 4-chlorobenzyl bromide (0.8g, 3.90mmol) in dry DMF (10 ml) was added sodium hydride (0.17g, 4.3 mmol, 60% dispersion in oil). The mixture was
5 allowed to warm slowly to ambient temperature over 18h. Water (50ml) was added and the mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated. Purification by flash column chromatography (DCM:ethyl acetate 95:5) of the residue afforded the product (1.56g, 75%). ¹H NMR 7.30 (4H, m), 5.40 and 5.25
10 (1H, 2xbr s), 4.80 (2H, s), 3.75 (1H, br s), 3.29 (2H, m), 2.84 (2H, br s), 1.92-1.39 (26H, m).

Step c *N*-(4-Chlorobenzyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product from Example 107 step b replacing the product of Example 97 step e. ¹H NMR 7.31 (4H, m), 4.50
15 (1H, br s), 4.18 (2H, s), 3.14 (1H, m), 3.07 (1H, m), 2.89 (1H, m), 2.33 (3H, s), 2.25 (2H, m), 1.79-1.43 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 46.26, H 6.44, N 10.63. C₁₅H₂₅Cl₂N₃O₂S. 0.3 mol water requires C 46.46, H 6.65, N 10.84.

20 **Example 108**

N-Benzyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

Step a *N*-Benzyl-*N'*-(*tert*-butoxycarbonyl)-sulfamide. The title compound was prepared as in Example 107 step a with benzylamine replacing the product of Example 91 step f.

25 **Step b** *N*-Benzyl-*N'*-(*tert*-butoxycarbonyl)-*N'*-(3-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide. To an ice-cooled solution of the product from Example 91 step e (0.9g, 3.9mmol) and the product of step a (1.22g, 3.9mmol) and triphenylphosphine (1.33g, 5.07mmol) in THF (10ml) was added a solution of diethyl azodicarboxylate (0.87ml, 5.07mmol) in THF (3ml). The yellow solution was allowed
30 to warm to ambient temperature and stirred for 2h. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate 70:30) to isolate the title compound (1.7g, 88%). ¹H NMR 7.33 (5H, m), 5.60 (1H, br s), 4.13 (2H, m), 3.80 (1H, br s), 3.59 (2H, m), 3.30 (2H, m), 1.84-1.44 (26H, m).

Step c *N-Benzyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide*. The title compound was prepared as in Example 97 step f with the product from Example 108 step b replacing the product of Example 97 step e. ¹H NMR 7.31 (5H, m), 4.60 (1H, br s), 4.21 (2H, s), 3.23 (1H, m), 3.05 (1H, m), 2.93 (1H, m), 2.40 (3H, s), 2.35 (2H, m), 1.83-1.48 (8H, m). Found C 56.00, H 8.10, N 12.93. C₁₅H₂₅N₃O₂S·0.6H₂O requires C 55.90, H 8.20, N 13.04.

Example 109

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)-sulfamide

Step a *3-(1-(tert-Butoxycarbonyl)-pyrrolidin-2R-yl)-propan-1-ol*. The title compound was prepared as in Example 91 steps a-e with N-(tert-butoxycarbonyl)-D-proline replacing N-(tert-butoxycarbonyl)-L-proline in step a.

Step b *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-sulfamide*. The title compound was prepared as in Example 107 step a with 4-chlorobenzylamine replacing the product from Example 91 step f.

Step c *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2R-yl)-propyl)-sulfamide*. The title compound was prepared as in Example 108 step b using the products derived from Example 109 steps a and b.

Step d *N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)-sulfamide*. The title compound was prepared as in Example 97 step f with the product from Example 108 step c replacing the product of Example 97 step e. ¹H NMR 7.34 (4H, m), 4.30 (1H, br s), 4.20 (2H, s), 3.08 (2H, m), 2.93 (1H, m), 2.34 (3H, s), 2.27 (2H, m), 1.78-1.50 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 45.93, H 6.66, N 10.74. C₁₅H₂₅ClN₃O₂S·0.53H₂O requires C 45.97, H 6.70, N 10.72.

Example 110

N-Cyclohexyl-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with cyclohexylmethylamine replacing benzylamine in step a. ¹H NMR 4.06 (1H, t), 3.07 (2H, m), 2.98 (1H, m), 2.87 (2H, t), 2.32 (3H, s), 2.23 (2H, m), 1.77-1.46 (14H, m), 1.21 (3H, m), 0.95 (2H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.98, H 9.39, N 11.38; C₁₅H₃₂ClN₃O₂S·1.13H₂O requires C 48.13, H 9.23, N 11.22.

Example 111

N-(2-(4-Chlorophenyl)-ethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 2-(4-

- 5 chlorophenyl)ethylamine replacing benzylamine in step a. ¹H NMR 7.28 (2H, m), 7.16 (2H, d), 4.05 (1H, br s), 3.28 (2H, m), 3.12 (1H, m), 2.96 (1H, m), 2.85 (3H, m), 2.31 (3H, s), 2.21 (2H, m), 1.76-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 45.29, H 6.98, N 10.10. C₁₆H₂₇Cl₂N₃O₂S·1.47H₂O requires C 45.45, H 7.14, 10 N 9.94.

Example 112

N-(4-Chlorophenyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 4-chloroaniline replacing

- 15 benzylamine in step a. ¹H NMR 7.27 (2H, m), 7.12 (2H, m), 3.08 (2H, m), 2.85 (1H, m), 2.26 (2H, m), 2.24 (3H, s), 1.75-1.47 (8H, m). Found C 47.82, H 6.72, N 12.09. C₁₄H₂₂ClN₃O₂S·1.0H₂O requires C 48.01, H 6.92, N 12.00.

Example 113

20 *N*-(4-Bromobenzyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

The title compound was prepared as in Example 107 with 4-bromobenzyl bromide

replacing 4-chlorobenzyl bromide, in step b. ¹H NMR 7.46 (2H, d), 7.23 (2H, d), 4.70

(1H, br s), 4.14 (2H, s), 3.12 (1H, m), 3.02 (1H, m), 2.88 (1H, m), 2.32 (3H, s), 2.24

(2H, m), 1.78-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen

- 25 chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 41.91, H 6.17, N 9.59. C₁₅H₂₅BrClN₃O₂S requires C 42.21, H 5.90, N 9.85.

Example 114

N-(4-Iodobenzyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

- 30 The title compound was prepared as in Example 107 with 4-iodobenzyl bromide replacing 4-chlorobenzyl bromide, in step b. ¹H NMR 7.67 (2H, d), 7.11 (2H, d), 4.50 (1H, br s), 4.15 (2H, s), 3.12 (1H, m), 3.04 (1H, m), 2.90 (1H, m), 2.32 (3H, s), 2.29 (2H, m), 1.78-1.42 (8H, m). Found C 40.77, H 5.79, N 9.41. C₁₅H₂₄IN₃O₂S·0.35H₂O requires C 40.61, H 5.61, N 9.47.

Example 115

N-(4-Chlorobenzyl)-*N'*-(2-(1-methyl-pyrrolidin-2*S*-yl)-ethyl)-sulfamide

The title compound was prepared as in Example 107, with the product from Example 97 step d replacing the product of Example 91 step f in step a. ¹H NMR 7.31 (4H, m), 4.60 (1H, br s), 4.18 (2H, s), 3.20 (1H, m), 3.05 (2H, m), 2.41 (1H, m), 2.32 (3H, s), 2.18 (1H, m), 1.86-1.58 (6H, m). Found C 50.46, H 6.75, N 12.42. C₁₄H₂₂ClN₃O₂S requires C 50.67, H 6.68, N 12.66.

Example 116

N-(4-Chlorobenzyl)-*N'*-(4-(1-methyl-pyrrolidin-2*S*-yl)-butyl)-sulfamide

Step a 2*S*-(4-Amino-butyl)-pyrrolidine-1-carboxylic acid tert-butyl ester. The title compound was prepared as in Example 97 steps b-d with the product of Example 91 step e replacing the product of Example 97 step a. ¹H NMR 3.70 (1H, m), 3.30 (2H, m), 2.70 (2H, t), 1.86- 1.21 (21H, m).

Step b *N*-tert-Butoxycarbonyl-*N'*-(4-(1-(tert-butoxycarbonyl)-pyrrolidin-2*S*-yl)-butyl)-sulfamide. The title compound was prepared as in Example 107 step a with the product from step a replacing the product of Example 91 step f. ¹H NMR 7.50 (1H, br s), 5.17 and 4.50 (1H, 2xbr s), 3.75 (1H, br s), 3.30 (2H, m), 3.08 (2H, m), 1.88-1.31 (28H, m).

Step c *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-(4-(1-(tert-butoxycarbonyl)-pyrrolidin-2*S*-yl)-butyl)-sulfamide. The title compound was prepared as Example 107 step b with the product from step b replacing the product of Example 107 step a. ¹H NMR 7.32 (4H, m), 5.23 (1H, t), 4.80 (2H, s), 3.78 (1H, br s), 3.31 (2H, m), 2.80 (2H, m), 1.82-1.49 (6H, m), 1.49 (9H, s), 1.46 (9H, s), 1.25 (4H, m).

Step d *N*-(4-Chlorobenzyl)-*N'*-(4-(1-methyl-pyrrolidin-2*S*-yl)-butyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product of step c replacing the product of Example 97 step e. ¹H NMR 7.33 (4H, m), 4.60 (1H, br s), 4.30 (1H, br s), 4.20 (2H, s), 3.22 (1H, m), 3.03 (2H, t), 2.41 (3H, s), 2.29-1.33 (12H, m). The hydrochloride salt was prepared in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 48.11, H 6.92, N 10.29. C₁₆H₂₇Cl₂N₃O₂S requires C 48.48, H 6.87, N 10.60.

Example 117

N-(4-Chlorobenzyl)-*N'*-(5-(1-methyl-pyrrolidin-2*S*-yl)-pentyl)-sulfamide

Step a *N*-(4-Chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(5-(1-(tert-butoxycarbonyl)-pyrrolidin-2*S*-yl)-pentyl)-sulfamide. The title compound was prepared as in Example

- 5 108 step b using the products derived from Example 105 step b and Example 109 step b. ¹H NMR 7.33 (2H, m), 7.26 (2H, m), 5.63 (1H, t), 4.12 (2H, d), 3.72 (1H, m), 3.57 (2H, m), 3.30 (2H, m), 1.91-1.24 (30H, m).

Step b *N*-(4-Chlorobenzyl)-*N'*-(5-(1-methyl-pyrrolidin-2*S*-yl)-pentyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product of step a

- 10 replacing the product of Example 97 step e. ¹H NMR 7.32 (4H, m), 4.60 (1H, br s), 4.19 (3H, s), 3.05 (1H, m), 3.00 (2H, m), 2.31 (3H, s), 2.16-1.23 (14H, m). Found C 54.33, H 7.61, N 11.04. C₁₇H₂₈ClN₃O₂S requires C 54.60, H 7.55, N 11.24.

Example 118

- 15 *N*-(4-Chlorobenzyl)-*N'*-(3-(1-(3-(4-chlorophenyl)propyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 4-chlorobenzylamine replacing benzylamine in step a, and 3-(4-chlorophenyl)propan-1-al replacing aqueous formaldehyde in step c. ¹H NMR 7.30 (6H, m), 7.20 (2H, d), 4.43 (1H, br s), 4.16 (2H, br s), 3.18 (1H, m), 3.02 (1H, m), 2.89 (1H, m), 2.75-2.50 (3H, m), 2.30 (1H, m), 2.11 (2H, m), 1.87-1.36 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.46, H 6.39, N 7.76. C₂₃H₃₂Cl₂N₃O₂S·0.9H₂O requires C 51.46, H 6.34, N 7.83%.

25 **Example 119**

N-(4-Chlorobenzyl)-*N'*-(3-(1-(iso-butyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 4-chlorobenzylamine replacing benzylamine in step a, and iso-butyraldehyde replacing aqueous

- 30 formaldehyde in step c. ¹H NMR 7.31 (4H, m), 5.60 (1H, br s), 4.54 (1H, br s), 4.17 (2H, br s), 3.16 (1H, m), 3.03 (1H, m), 2.93 (1H, m), 2.42-1.48 (13H, m), 0.91 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.59, H 7.39, N 9.81. C₁₈H₃₁Cl₂N₃O₂S requires C 50.94, H 7.36, N 9.90.

Example 120

N-(4-Chlorobenzyl)-*N,N'*-dimethyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide.

Step a *N*-(4-Chlorobenzyl)-*N,N'*-dimethyl-*N'*-(3-(1-*tert*-butoxycarbonyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide. To a solution of *N*-(4-chlorobenzyl)-*N'*-(3-(pyrrolidin-2*S*-yl)-propyl)sulfamide (1.03g, 2.87mmol) in 1,4-dioxan (10ml) was added di-*tert*-butyldicarbonate (625mg, 2.87mmol) and the reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure and the residue dissolved in chloroform (50ml) and washed sequentially with water (50ml), aqueous citric acid (10%, 50ml) and brine (50ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). The product was dissolved in DMF (8ml) and cooled in ice. The solution was treated sequentially with iodomethane (0.253ml, 4.06mmol) and sodium hydride (60% dispersion in mineral oil, 185mg, 4.63mmol). The suspension was allowed to warm to ambient temperature over 18h and then water (75ml) was added. The aqueous phase was extracted with ethyl acetate (75ml) and the organic phase was subsequently washed twice with brine (75ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (3:2 hexane:ethyl acetate) to obtain the title compound (686mg, 52%). ¹H NMR 7.35-7.27 (4H, m), 4.27 (2H, s), 3.77 (1H, m), 3.34-3.21 (4H, m), 2.83 (3H, s), 2.65 (3H, s), 1.94-1.24 (17H, m).

Step b *N*-(4-Chlorobenzyl)-*N,N'*-dimethyl-*N'*-(3-(pyrrolidin-2*S*-yl)-propyl)-sulfamide. The title compound was prepared as in Example 90 step d with the product from Example 120 step a replacing the product of Example 90 step c. ¹H NMR 7.35-7.17 (4H, m), 4.27 (2H, s), 3.24-3.18 (2H, m), 3.01-2.95 (2H, m), 2.89-2.86 (1H, m), 2.83 (3H, s), 2.66 (3H, s), 1.78-1.24 (9H, m).

Step c *N*-(4-Chlorobenzyl)-*N,N'*-dimethyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide. The title compound was prepared as in Example 90 step e with the product from Example 120 step b replacing the product of Example 90 step d. The oil was treated with hydrogen chloride in 1,4-dioxan and the solvent removed *in vacuo*. ¹H NMR (free base) 7.35-7.27 (4H, m), 4.28 (2H, s), 3.21 (2H, t, 7.2), 3.10-3.04 (1H, m), 2.83 (3H, s), 2.63 (3H, s), 2.31 (3H, s), 2.20-1.30 (10H, m). Microanalysis found C 49.41 H 7.60 N 10.18. C₁₇H₂₉ClN₃O₂S requires C 49.75 H 7.37 N 10.24.

Example 121

N-(4-Chlorobenzyl)-*N*-methyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

Step a *N*-(4-Chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide. The title compound was prepared as in Example 108 step b using the products derived from Example 91 step e and Example 109 step b as substrates.

Step b *N*-(4-Chlorobenzyl)-*N*-methyl-*N'*-(tert-butoxycarbonyl)-*N'*-(3-(1-(tert-butoxycarbonyl)-pyrrolidin-2*S*-yl)-propyl)-sulfamide. To a solution of the product of step a (1.0g, 1.9mmol) in DMF (5ml) was added sodium hydride (90mg, 2.26mmol; 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the stirring was continued for 1h. Iodomethane (0.13ml, 2.1mmol) was added and the stirring was continued overnight. Water (50ml) was added and the product was extracted with ethyl acetate (2x30ml), the organic phase was dried, the solvent was evaporated. Flash column chromatography (hexane:ethyl acetate 70:30) afforded the title compound (0.94g, 91%). ¹H NMR 7.28 (4H, m), 4.39 (2H, s), 3.70 (3H, m), 3.30 (2H, m), 2.75 (3H, s), 1.85-1.26 (26H, m).

Step c *N*-(4-Chlorobenzyl)-*N*-methyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide The title compound was prepared as in Example 97 step f with the product from Example 121 step b replacing the product of Example 97 step e. ¹H NMR 7.31 (4H, m), 4.26 (2H, s), 3.11 (2H, m), 2.95 (1H, m), 2.67 (3H, s), 2.33 (3H, s), 2.22 (2H, m), 1.78-1.44 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 122

N-(4-Chlorobenzyl)-*N'*-methyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide

Step a *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-methyl-*N'*-(3-(1-(tert-butoxycarbonyl)pyrrolidin-2*S*-yl)propyl)-sulfamide. The title compound was prepared as in Example 121 step b with the product from Example 107 step b replacing the product of Example 121 step a. ¹H NMR 7.31 (4H, m), 4.82 (2H, s), 3.80 (1H, br s), 3.30 (2H, m), 3.13 (2H, m), 2.79 (3H, s), 1.87-1.26 (26H, m).

Step b *N*-(4-Chlorobenzyl)-*N'*-methyl-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product from Example 122 step a replacing the product of Example 97 step e. ¹H NMR 7.32

(4H, m), 4.50 (1H, m), 4.16 (1H, br s), 3.07 (3H, m), 2.79 (3H, s), 2.30 (3H, s), 1.76-1.29 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

5 Example 123

N-(4-Chlorobenzyl)-*N'*-(methoxycarbonylmethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide.

Step a *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-(methoxycarbonylmethyl)-*N'*-(3-(1-(tert-butoxycarbonyl)pyrrolidin-2*S*-yl)propyl)-sulfamide. The title compound
10 was prepared as in Example 122 step a with methyl bromoacetate replacing iodomethane. ¹H NMR 7.31 (4H, m), 4.82 (2H, s), 4.05 (2H, s), 3.70 (4H, br s), 3.27 (4H, m), 1.87-1.26 (26H, m).

Step b *N*-(4-Chlorobenzyl)-*N'*-(methoxycarbonylmethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide.

15 The title compound was prepared as in Example 97 step f with the product from Example 123 step a replacing the product of Example 97 step e. ¹H NMR 7.31 (4H, m), 5.05 (1H, br s), 4.30 (2H, s), 4.08 (2H, s), 3.75 (3H, s), 3.24 (2H, m), 3.09 (1H, m), 2.30 (3H, s), 2.177-1.22 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

20 Microanalysis found 45.81 H 6.61 N 8.90 C₁₈H₂₉Cl₂N₃O₄S·0.97H₂O requires C 45.82 H 6.61 N 8.90.

Example 124

N-(4-Chlorobenzyl)-*N'*-(2-hydroxyethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-
25 sulfamide. The title compound was prepared as in Example 88 step c with the product from Example 123 step b replacing the product of Example 88 step b. ¹H NMR 7.29 (4H, m), 4.17 (2H, s), 3.67 (3H, m), 3.35 (2H, m), 3.20 (2H, m), 3.02 (1H, m), 2.27 (3H, s), 2.16-1.20 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

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Example 125

N-(4-Chlorobenzyl)-*N'*-(3-phthalimido-propyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide. To an ice-cooled stirred solution of the product from Example 107 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride

(60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed the reaction mixture was stirred at ambient temperature for 1h. N-(3-Bromopropyl)phthalimide (295mg, 1.10mmol) added and the reaction mixture was heated at 100°C for 2h and then allowed to cool. The reaction mixture was diluted with water (30ml) and extracted twice with ethyl acetate (30ml) and the aqueous phase was discarded. The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue was treated with trifluoroacetic acid (5ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was evaporated at reduced pressure and the residue was dissolved in DCM (30ml). The organic phase was washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (5ml) and treated sequentially with aqueous formaldehyde (37%, 0.20ml) and sodium triacetoxyborohydride (300mg, 1.42mmol). The resultant suspension was stirred at ambient temperature for 1h and then was quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent evaporated at reduced pressure. The residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ¹H NMR 7.83 (2H, m), 7.71 (2H, m), 7.30 (4H, m), 4.75 (1H, br s), 4.15 (2H, s), 3.71 (2H, m), 3.25 (2H, m), 3.16 (2H, m), 3.02 (1H, m), 2.26 (3H, s), 2.10-1.10 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 54.50 H 6.11 N 9.56 C₂₆H₃₄Cl₂N₄O₄S requires C 54.83 H 6.02 N 9.84.

25

Example 126

N-(4-Chlorobenzyl)-*N'*-(3-amino-propyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide. To a stirred solution of the product of Example 125 (200mg, 0.38mmol) in ethanol (2ml) was added hydrazine hydrate (0.06ml) and the reaction mixture was heated at reflux for 1h. The solvent was removed at reduced pressure, the residue was suspended in chloroform (10ml) and the solid removed by filtration. The filtrate was evaporated at reduced pressure and the residue evaporated thrice from chloroform (10ml) to afford the title compound (125mg, 82%). ¹H NMR 7.28 (5H, m), 4.12 (2H, s), 3.24 (2H, m), 3.2-2.5 (2H, vbr s), 3.15 (2H, m), 3.03 (1H, m), 2.72 (2H, m), 2.27

30

(3H, s), 2.14-1.00 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 127

5 *N*-(4-Chlorobenzyl)-*N'*-(methyamidomethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide

Step a *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-(carboxymethyl)-*N'*-(3-(1-(tert-butoxycarbonyl)pyrrolidin-2*S*-yl)propyl)-sulfamide. To a solution of the product of Example 123 step a (3.54g, 5.86mmol) in THF (10ml) was added an aqueous
10 solution of lithium hydroxide (1M, 10ml) and the resultant reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure to half the initial volume and diluted with aqueous hydrochloric acid (2M, 5ml) and water (50ml). The aqueous phase was extracted twice with ethyl acetate (50ml) and the combined organic layers were washed with brine (50ml) and dried over
15 anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound. ¹H NMR (DMSO-*d*₆) 13.0 (1H, br s), 7.41(2H, d, 8.4), 7.30 (2H, d, 8.4), 4.75 (2H, s), 4.03 (2H, s), 3.75 (1H, m), 3.18 (4H, m), 2.00-1.10 (22H, m).

Step b *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-(methyamidomethyl)-*N'*-(3-(1-(tert-butoxycarbonyl)pyrrolidin-2*S*-yl)propyl)-sulfamide. To an ice-cooled solution of the product from Example 127 step a (590mg, 1.00mmol) in DCM (20ml) was added
20 N-hydroxysuccinimide (126mg, 1.10mmol). The coolant was removed and the reaction stirred at ambient temperature, and then treated with dicyclohexylcarbodiimide (233mg, 1.11mmol), and stirred at this temperature for 1h.
25 The suspension was filtered to remove the solid and methylamine was bubbled through the filtrate for 5 minutes. The reaction mixture was stirred at ambient temperature for a further 1h and then diluted with DCM (20ml). The reaction mixture washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric acid(1M, 20ml) and water (20ml). The organic phase
30 was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure to afford the title compound (650mg, q). ¹H NMR 7.31 (4H, m), 6.70 (1H, br s), 4.84 (2H, s), 3.91 (2H, s), 3.70 (1H, m), 3.30-3.17 (4H, m), 2.81 (3H, d, 4.5), 1.47 (18H, s), 1.90-1.18 (10H, m).

Step c *N*-(4-Chlorobenzyl)-*N'*-(methanamidomethyl)-*N'*-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product from Example 127 step b replacing the product of Example 97 step e. ¹H NMR 7.30 (4H, m), 6.50(1H, m), 4.69 (1H, s), 4.23 (2H, s), 3.85 (2H, s), 3.17 (2H, m), 3.03 (1H, m), 2.80 (3H, s), 2.28 (3H, s), 2.17-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 46.63 H 7.04 N 11.93 C₁₈H₃₀Cl₂N₄O₃S·0.5H₂O requires C 46.75 H 6.76 N 12.11.

10 **Example 128**

N-(4-Chlorobenzyl)-*N'*-(dimethanamidomethyl)-*N'*-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

The title compound was prepared as in Example 127 with dimethylamine replacing methylamine in step b. ¹H NMR 7.29 (4H, m), 6.25(1H, m), 4.30 (2H, d, 5.4), 4.14 (2H, s), 3.24 (2H, m), 3.04 (1H, m), 2.96 (3H, s), 2.93 (3H, s), 2.28 (3H, s), 2.15-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 48.48 H 7.18 N 11.67 C₁₉H₃₂Cl₂N₄O₃S requires C 48.81 H 6.90 N 11.98.

20 **Example 129**

N-(4-Chlorobenzyl)-*N'*-(4-chlorobenzylamidomethyl)-*N'*-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

Step a *N*-(tert-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-*N'*-(4-chlorobenzylamidomethyl)-*N'*-(3-(1-(tert-butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide. To an ice-cooled solution of the product of Example 127 step a (590mg, 1.00mmol), 4-chlorobenzylamine (0.133ml, 1.10mmol), N-hydroxybenzotriazole hydrate (168mg, 1.10mmol) and 4-dimethylaminopyridine (20mg, 0.16mmol) in DCM (20ml) was added EDC (211mg, 1.10mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 16h. The reaction mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric acid (1M, 20ml) and water (20ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure to afford the title compound (675mg, 95%). ¹H NMR 7.30 (9H, m), 4.83 (2H, s), 4.42

(2H, d, 6), 3.98 (2H, s), 3.60 (1H, m), 3.50-3.00 (4H, m), 1.45 (9H, s), 1.42 (9H, s), 2.0-1.0 (8H, m).

- Step b** *N*-(4-Chlorobenzyl)-*N'*-(4-chlorobenzylamidomethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product from Example 129 step a replacing the product of Example 97 step e. ¹H NMR 7.32-7.16 (9H, m), 6.81 (1H, m), 4.36 (2H, d, 6), 4.19 (2H, s), 3.84 (2H, s), 3.15 (2H, m), 3.00 (1H, m), 2.24 (3H, s), 2.13-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 51.22 H 6.10 N 10.04
- 10 C₂₄H₃₃Cl₃N₄O₃S requires C 51.11 H 6.10 N 9.93.

Example 130

N-(4-Chlorobenzyl)-*N'*-(benzyloxycarbonylmethyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide

- 15 The title compound was prepared as in Example 122 with benzyl bromoacetate replacing iodomethane in step a. ¹H NMR 7.39-7.25 (9H, m), 5.18 (2H, s), 4.26 (2H, d, 6), 4.11 (2H, s), 3.27 (2H, m), 3.08 (1H, m), 2.31 (3H, s), 2.18-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 47.70 H 6.99 N 6.74
- 20 C₂₄H₃₃Cl₂N₃O₄S·4H₂O requires C 47.84 H 6.86 N 6.97.

Example 131

- N*-(4-Chlorobenzyl)-*N'*-(3-(4-chlorophenyl)propyl)-*N'*-(3-(1-methyl-pyrrolidin-2*S*-yl)propyl)-sulfamide. To an ice-cooled stirred solution of the product of Example 107 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed and methanesulfonic acid 3-(4-chlorophenyl)-propyl ester (261mg, 1.10mmol) was added. The reaction mixture was heated at 100°C for 3h and then allowed to cool. The reaction mixture was diluted with water (30ml) and extracted with ethyl acetate (30ml). The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (5:4:1 Hexane:DCM:ethyl acetate). The purified material was treated with trifluoroacetic acid (2ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was
- 25
- 30

evaporated at reduced pressure and the residue dissolved in DCM (30ml). The organic phase was washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (3ml) and treated sequentially with aqueous formaldehyde (37%, 0.06ml) and sodium triacetoxymethylborohydride (160mg, 0.75mmol). The resultant suspension was stirred at ambient temperature for 1h, quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ¹H NMR 7.32-7.08 (8H, m), 4.62 (1H, br s), 4.12 (2H, s), 3.12 (4H, m), 3.04 (1H, m), 2.59 (2H, m), 2.15 (3H, s), 2.20-1.20 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 53.62 H 6.41 N 7.55 C₂₄H₃₄Cl₃N₃O₂S requires C 53.88 H 6.41 N 7.85.

15 Example 132

N-(4-Chlorobenzyl)-*N'*-(3-(4*R*-hydroxy-1-methyl-pyrrolidin-2*S*-yl)-propyl)-sulfamide

Step a 2*S*-(Methoxy-methyl-carbamoyl)-4*R*-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester. The title compound was prepared as in Example 91 step a with *N*-(tert-butoxycarbonyl)-L-*trans*-4-hydroxyproline replacing with *N*-(tert-butoxycarbonyl)-L-proline. ¹H NMR (DMSO-d₆) 5.01 (1H, d), 4.64 (1H, m), 4.22 (1H, br s), 3.71 and 3.68 (3H, 2xs), 3.30 (2H, m), 3.10 and 3.08 (3H, 2xs), 2.20 (1H, m), 1.78 (1H, m), 1.37 and 1.31 (9H, 2xs).

Step b 2*S*-Formyl-4*R*-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester. The title compound was prepared as in Example 91 step b with the product from Example 132 step a replacing the product of Example 91 step a. ¹H NMR 9.45 and 9.44 (1H, 2xbr s), 4.49 (1H, br s), 4.13 and 4.11 (2H, 2xm), 3.58 (2H, m), 2.16-1.97 (3H, m), 1.48 and 1.44 (9H, 2xs).

Step c 3-(1-(tert-Butoxycarbonyl)-4*R*-hydroxy-pyrrolidin-2*S*-yl)-acrylic acid ethyl ester. The title compound was prepared as in Example 91 step c with the the product from Example 132 step b replacing the product of Example 91 step b. ¹H NMR (DMSO-d₆) 6.80 (1H, dd), 5.86 (1H, d), 4.50 (1H, br s), 4.30 (1H, m), 4.16 (2H, m), 3.53 (2H, m), 2.17 (1H, m), 1.87 (2H, m), 1.43 (9H, s), 1.26 (3H, t).

Step d 3-(1-(tert-Butoxycarbonyl)-4*R*-hydroxy-pyrrolidin-2*S*-yl)-propionic acid ethyl ester. The title compound was prepared as in Example 91 step d with the the product

from Example 132 step c replacing the product of Example 91 step c. ¹H NMR 4.40 (1H, m), 4.11 (2H, m), 3.97 (1H, m), 3.94 (2H, m), 2.28 (2H, t), 2.07 (2H, m), 1.78 (3H, m), 1.47 (9H, s), 1.25 (3H, t).

Step e 3-(1-(tert-Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propan-1-ol. The title compound was prepared as in Example 88 step c with the the product from Example 132 step d replacing the product of Example 88 step b. ¹H NMR (DMSO-*d*₆) 4.80 (1H, d), 4.35 (1H, t), 4.15 (1H, m), 3.72 (1H, m), 3.35 (2H, m), 3.23 (2H, m), 1.90-1.50 (4H, m), 1.38 (9H, s), 1.16 (2H, m).

Step f N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propyl)-sulfamide. The title compound was prepared as in Example 108 step b using the products derived from Example 109 step b and Example 132 step e. ¹H NMR (DMSO-*d*₆) 8.26 (1H, s), 7.33 (4H, m), 4.81 (1H, d), 4.06 (3H, m), 3.68 (1H, m), 3.30 (2H, m), 1.90-1.22 (24H, m).

Step g N-(4-Chlorobenzyl)-N'-(3-(4R-hydroxy-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide. The title compound was prepared as in Example 97 step f with the product from Example 132 step f replacing the product of Example 97 step e. The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. ¹H NMR (DMSO-*d*₆) 10.60 (1H, br s), 7.39 (5H, m), 6.98 (1H, t), 5.50 (1H, br s), 4.33 (1H, br s), 4.01 (2H, d), 3.72 (1H, m), 3.45 (1H, m), 3.30 (1H, m), 2.83 (5H, m), 2.07-1.45 (6H, m).

Example 133

N-(4-Chlorobenzyl)-N'-(3-(4R-(4-chlorobenzoyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a 3-(1-(tert-Butoxycarbonyl)-4R-(4-chlorobenzoyloxy)-pyrrolidin-2S-yl)-propionic acid ethyl ester. To a solution of the product from Example 132 step d (0.90g, 3.13mmol) in DMF (10 ml) was added sodium hydride (0.15g, 3.76mmol, 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the mixture was stirred for 1h, 4-chlorobenzyl bromide was added and the stirring was continued for 16h. The reaction was quenched with water (40ml) and the product was extracted with ethyl acetate (2x20ml), the organic extracts were dried over anhydrous magnesium sulfate, the solvent was evaporated. Purification by flash column chromatography (hexane:ethyl acetate 70:30) afforded the product as a colourless oil (0.36g, 28%). ¹H NMR 7.30 (4H, m), 4.50 (2H, m),

4.11 (3H, m), 3.96 (1H, m), 3.70 and 3.50 (1H, 2xbr s), 3.67 (1H, br s), 2.28 (2H, m), 2.12 (2H, m), 1.76 (2H, m), 1.47 and 1.45 (9H, 2xs), 1.25 (3H, t).

Step b *3-(1-(tert-Butoxycarbonyl)-4R-(4-chlorobenzoyloxy)-pyrrolidin-2S-yl)-propan-1-ol*. The title compound was prepared as in Example 88 step c with the product from

- 5 Example 133 step a replacing the product of Example 88 step b. ¹H NMR 7.30 (4H, m), 4.46 (2H, br s), 4.10 (1H, m), 3.96 (1H, br s), 3.67 (3H, m), 3.39 (1H, m), 2.13 (1H, m), 1.82 (5H, m), 1.42 (11H, m).

- Step c** *N-(4-Chlorobenzyl)-N'-(tert-butoxycarbonyl)-N'-(3-(1-(tert-butoxycarbonyl)-4R-(4-chlorobenzoyloxy)-pyrrolidin-2S-yl)-propyl)-sulfamide*. The title compound was
10 prepared as in Example 108 step b using the products derived from Example 109 step b and Example 133 step b. ¹H NMR 7.30 (8H, m), 5.70 (1H, br s), 4.45 (2H, br s), 4.12 (2H, d), 4.06 (1H, m), 3.96 (1H, br s), 3.60 (2H, m), 3.30 (1H, m), 1.90-1.22 (24H, m).

- Step d** *N-(4-Chlorobenzyl)-N'-(3-(4R-(4-Chlorobenzoyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide*. The title compound was prepared as in Example 97 step f with
15 the product from Example 133 step c replacing the product of Example 97 step e. ¹H NMR 7.30 (8H, m), 4.63 (1H, br s), 4.43 (2H, m), 4.18 (2H, d), 4.11 (1H, m), 3.52 (1H, m), 3.04 (1H, m), 3.04 (1H, m), 2.92 (1H, m), 2.63 (1H, m), 2.43 (1H, m), 2.41 (3H, s), 2.20 (1H, br s), 1.97 (1H, m), 1.77 (1H, m), 1.55 (3H, m). The hydrochloride
20 salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.08, H 5.81, N 8.03. C₂₂H₃₀Cl₃N₃O₃S·0.2H₂O requires C 50.13, H 5.83, N 7.97.

Example 134

- 25 *N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)-sulfamide*. To an ice-cooled solution of the product from Example 109 step b (321mg, 1.00mmol), 1-(2-hydroxyethyl)pyrrolidine (0.152ml, 1.30mmol) and triphenylphosphine (393mg, 1.50mmol) in THF (2ml) was added in a single portion diethylazodicarboxylate (0.257ml, 1.50mmol). The coolant was removed and the reaction mixture was stirred
30 at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (25ml) and washed sequentially with water (20ml), twice with aqueous hydrochloric acid (2M, 25ml) and brine (25ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was dissolved in 1,4-dioxan (5ml) and treated with aqueous hydrochloric acid (2M, 5ml).

The resultant mixture was heated at reflux for 1h and then diluted with further aqueous hydrochloric acid (30ml). The aqueous was washed twice with diethyl ether (30ml) and then the pH was adjusted to 11 with ammonia (880). The now basic phase was extracted twice with chloroform (50ml) and then dried over anhydrous sodium sulfate.

- 5 The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (200:10:1 DCM:methanol:ammonia) to afford the title compound as a white solid (95mg, 30%). ¹H NMR 7.35-7.28 (4H, m), 6.0-4.5 (2H, br s), 4.20 (2H, s), 3.19 (2H, t, 5.7), 2.59 (2H, t, 5.7), 2.50-2.46 (4H, m), 1.73-1.67 (4H, m). Microanalysis found C 49.05 H 6.36 N 13.09 C₁₃H₂₀ClN₃O₂S requires C 49.13 H 6.34 N 13.22.
- 10

Example 135

- N*-(4-Chlorobenzyl)-*N'*-(3-pyrrolidin-1-yl-propyl)-sulfamide. A solution of 4-chlorobenzylamine (0.610ml, 5.00mmol), 1-(3-aminopropyl)pyrrolidine (0.632ml, 5.00mmol) and sulfamide (480mg, 4.99mol) was heated at reflux for 2h. The reaction was allowed to cool and partitioned between ethyl acetate (20ml) and water (20ml). The aqueous was discarded and the organic phase washed with water (20ml) and brine (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (100:10:1 DCM:methanol) to obtain the title compound as a white solid (365mg, 22%). ¹H NMR 7.35-7.28 (4H, m), 4.18 (2H, s), 3.15 (2H, t, 6), 2.61 (2H, t, 6), 2.51 (4H, br m), 1.82-1.67 (6H, m). Microanalysis found C 49.97 H 6.73 N12.50 C₁₄H₂₂ClN₃O₂S-0.26H₂O requires C 49.96 H 6.74 N 12.49.
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- 20

25 Example 136

N-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide

- Step a** *N*-(4-Chlorobenzyl)-methanesulfonamide. A solution of 4-chlorobenzylamine (12.20g, 86.2mmol) and triethylamine (14.4ml, 103.5mmol) in DCM (200ml) was cooled in an ice bath. Mesyl chloride (7.34ml, 94.9mmol) was added dropwise and the solution was stirred for 10min. The cold bath was removed and the solution stirred for a further 2h. The reaction was diluted with a equal volume of DCM and washed with 10% citric acid solution and brine. The solvent was evaporated and the residue recrystallised from hot ethyl acetate. The product was thus obtained as a colourless crystalline solid (15.34g, 81%).
- 30

Step b *N*-(*tert*-Butoxycarbonyl)-*N*-(4-chlorobenzyl)-methanesulfonamide. To a solution of *N*-(4-chlorobenzyl)-methanesulfonamide (15.30g, 69.6mmol) and di-*tert*-butyl-dicarbonate (18.27g, 83.6mmol) in DCM (150ml) was carefully added *N,N*-dimethylaminopyridine (848mg, 6.96mmol); there was immediate and vigorous effervescence. The solution was stirred for 30min, by which time effervescence had ceased. The solution was diluted to a total volume of 500ml with DCM and washed twice with 10% citric acid solution and then brine. The solvent was evaporated to give a yellow solid, which was recrystallised from hot propan-2-ol (100ml). The precipitate was collected by filtration and dried *in vacuo* at 50°C to afford the product as a colourless crystalline solid (19.70g, 89%).

Step c 3-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2*S*-yl)-propan-1-al. A solution of oxalyl chloride (1.2ml, 13.7mmol) in DCM (40ml) was cooled to -78°C and dimethylsulfoxide (1.9ml, 27.3mmol) was added dropwise with concomitant effervescence. The solution was stirred for 5 mins, by which time effervescence had ceased, and a solution of the product from Example 91 step e (2.6g, 11.4mmol) in DCM (30ml) was added. The solution was stirred for 20 mins, triethylamine (5.7ml, 41.0mmol) was added, the cold bath was removed and the resultant solution was stirred for 3h. The solution was washed with water (2x50ml), the organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane:ethyl acetate 70:30) to afford the aldehyde as an oil (2.16 g, 83%). ¹H NMR 9.77 (1H, t), 3.83 (1H, m), 3.30 (2H, m), 2.46 (2H, m), 1.99-1.26 (15H, m).

Step d *N*-(4-Chlorobenzyl)-4-(1-(*tert*-butoxycarbonyl)-pyrrolidin-2*S*-yl)-but-1-enesulfonamide. A solution of the product from step c (0.8g, 3.0mmol) in THF (10 ml) was cooled to -78°C, 1.0M potassium *tert*-butoxide (5.0ml, 5.0mmol) was added dropwise and the solution was stirred for 1h. A solution of the aldehyde from step c of this example (0.57g, 2.5mmol) in THF (10ml) was added and the solution was stirred overnight allowing the temperature to slowly warm to ambient temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30ml) and extracted with diethyl ether (2x15ml). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Purification by flash column chromatography (hexane:ethyl acetate 1:1) of the residue gave the titled product (0.65g, 62%). ¹H NMR 7.30 (4H, m), 6.75 (1H, m),

6.20 (1H, d), 4.74 (1H, m), 4.17 (2H, d), 3.77 (1H, m), 3.30 (2H, m), 2.20 (2H, m), 1.95-1.46 (15H, m).

Step f *N*-(4-Chlorobenzyl)-4-(1-(tert-butoxycarbonyl)-pyrrolidin-2S-yl)-butane sulfonamide. A round bottom flask containing the product of step e (0.27g, 0.63mmol), 10% palladium-on-charcoal (30mg) and THF:methanol 1:1 (10ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to afford the product as a colourless foam (0.21g, 78%). ¹H NMR 7.32 (4H, m), 5.10 and 4.90 (1H, 2xbr s), 4.27 (2H d), 3.75 (1H, m), 3.30 (2H, m), 2.90 (2H, m), 1.80-1.26 (19H, m).

Step g *N*-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide. The title compound was prepared as in Example 97 step f with the product from Example 136 step f replacing the product of Example 97 step e. ¹H NMR 7.30 (4H, m), 5.00 (1H br s), 4.27 (2H, d), 3.05 (1H, m), 2.92 (2H, m), 2.29 (3H, s), 2.16-1.22 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.36, H 6.91, N 6.92. C₁₆H₂₆Cl₂N₂O₂S·1.3H₂O requires C 47.56, H 7.11, N 6.93%.

Example 137

20 *N*-Cyclohexyl-methyl-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide.

The title compound was prepared as in Example 136, with cyclohexyl-methylamine replacing 4-chlorobenzylamine in step a. ¹H NMR 4.30 (1H, t), 3.10-2.91 (4H, m), 2.31 (3H, s), 2.16 (1H, m), 2.01-1.67 (13H, m), 1.45 (4H, m), 1.24 (4H, m), 0.94 (2H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.75, H 9.80, N 7.52. C₁₆H₃₃ClN₂O₂S·1.5H₂O requires C 50.55, H 9.55, N 7.37%.

Example 138

N-Adamantan-1-yl-methyl-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide.

30 The title compound was prepared according to the procedure of Example 136, with adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step a. ¹H NMR 4.28 (1H, t), 3.03 (3H, m), 2.74 (2H, d), 2.29 (3H, s), 2.12 (1H, m), 1.08-1.23 (26H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and

lyophilised from water and 1,4-dioxan. Found C 55.52, H 9.43, N 6.60.

C₂₀H₃₇ClN₂O₂S·1.5H₂O requires C 55.62, H 9.33, N 6.49 %.

Example 139

5 *N*-(4-Chlorobenzyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-sulfamide.

Step a. *N*-(4-Chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(1-pent-4-enyl)-sulfamide and *N*-(4-chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N,N'*-bis(1-pent-4-enyl)-sulfamide To a solution of the product of Example 109 step b (1.60g, 5.00mmol), 4-penten-1-ol (0.80ml, 7.50mmol) and triphenylphosphine (2.00g, 7.50mmol) in THF was added
10 diethylazodicarboxylate (1.30ml, 7.50mmol). The solution was kept at ambient temperature for 16h. The solvent was evaporated and the two products were separated by flash column chromatography (90:10 hexane:ethyl acetate) to obtain *N*-(4-chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(1-pent-4-enyl)-sulfamide (low R_f, 773mg, 40%) and *N*-(4-chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N,N'*-bis(1-pent-4-enyl)-
15 sulfamide (high R_f, 1.03g, 45%).

Step b. *N*-(4-Chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(1-butan-4-yl)-sulfamide. The title compound was prepared according to the procedure of Example 17, step c using the low R_f material from step a above as substrate.

Step c. *N*-(4-Chlorobenzyl)-*N'*-(tert-butoxycarbonyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-sulfamide. The title compound was prepared according to the procedure of Example
20 17, step d with the product of step b above replacing the product of Example 17 step c.

Step d. *N*-(4-Chlorobenzyl)-*N'*-(4-pyrrolidin-1-yl-butyl)-sulfamide. To a solution of the product of step c above (490mg, 1.10mmol) in dioxan (5ml) was added hydrogen chloride in dioxan (1ml, 4.00mmol) and the solution was stirred at ambient
25 temperature for 16h. The solvent was evaporated and the residue was dissolved in DCM (20ml). The organic phase was washed with 10% aqueous potassium carbonate (2x20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated to afford the title compound (270mg, 71%). ¹H NMR 7.31 (4H, m), 4.30 (1H, br s), 4.17 (2H, s), 2.98 (2H, t), 2.56 (4H, m), 2.49 (2H, t), 1.84 (4H, m), 1.63 (4H, m). Found C
30 52.03, H 7.04, N 11.82. C₁₅H₂₄ClN₃O₂S requires C 52.09, H 6.99, N 12.15%.

Example 140

N-(4-Chlorobenzyl)-*N,N'*-bis(4-pyrrolidin-1-yl-butyl)-sulfamide.

The high R_f product of Example 139 step a was converted to the title compound according to the procedure of Example 139, steps b-d. ^1H NMR 7.30 (4H, m), 4.32 (2H, s), 3.10 (2H, t), 2.95 (2H, m), 2.48 (10H, m), 2.38 (2H, t), 1.80 (8H, m), 1.63 (6H, m), 1.41 (2H, m). The bis-hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 48.42, H 7.80, N 9.94. $\text{C}_{23}\text{H}_{41}\text{Cl}_3\text{N}_4\text{O}_2\text{S} \cdot 1.4 \text{ mol H}_2\text{O}$ requires C 48.53, H 7.76, N 9.84%.

Example 141

N-(4-Chlorobenzyl)-*N'*-(5-pyrrolidin-1-yl-pentyl)-sulfamide.

10 The title compound was prepared according to the procedure of Example 139, using 5-hexen-1-ol in step a instead of 4-penten-1-ol. ^1H NMR 7.31 (4H, m), 4.80 (1H, br s), 4.17 (2H, s), 3.00 (2H, t), 2.55 (4H, m), 2.47 (2H, t), 1.80 (4H, m), 1.52 (4H, m), 1.36 (2H, m). Found C 52.14, H 7.46, N 11.49. $\text{C}_{16}\text{H}_{26}\text{ClN}_3\text{O}_2\text{S} \cdot 0.5 \text{ mol H}_2\text{O}$ requires C 52.17, H 7.37, N 11.41%.

15

Example 142

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-cyclohexyl-ethanesulfonamide.

The title compound was prepared according to the procedure of Example 97, steps e and f, with the modification that the product of Example 91 step f and 2-cyclohexyl-ethanesulfonyl chloride was used in step e instead of the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride. ^1H NMR 3.11 (2H, m), 2.98 (3H, m), 2.32 (3H, s), 2.21 (2H, m), 1.86-0.90 (21H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.78, H 9.67, N 7.45. $\text{C}_{16}\text{H}_{33}\text{ClN}_2\text{O}_2\text{S} \cdot 1.4 \text{ mol H}_2\text{O}$ requires C 50.86, H 9.54, N 7.41%.

25

Example 143

N-(3-(1-iso-Butyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-methanesulfonamide.

30 The title compound was prepared according to the procedure of Example 97, steps e and f, with the product of Example 91 step f replacing the product of Example 97 step d in step e and iso-butyraldehyde replaced aqueous formaldehyde in step f. ^1H NMR 7.34 (4H, m), 6.00 (1H, br s), 4.18 (2H, s), 3.11 (1H, m), 2.98 (1H, m), 2.88 (1H, m), 2.35 (2H, m), 2.00 (1H, m), 1.95 (1H, m), 1.78-1.48 (9H, m), 0.90 (6H, t). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised

from water and 1,4-dioxan. Found C 52.49, H 7.67, N 6.75. $C_{18}H_{30}Cl_2N_2O_2S$ requires C 58.81, H 7.39, N 6.84%.

References.

- 5 1. J. Med. Chem 1994, 314.
2. WO 97/29092

Histamine H_3 functional assay - guinea pig ileum

The biological activity of the compounds of the examples was measured using the ileal longitudinal muscle, myenteric plexus assay described by Paton and Aboo Zar (*J. Physiol.* 1968, **194**, 13-33). Male Dunkin-Hartley guinea pigs (250-300g) were employed. Briefly, a 50cm portion of ileum proximal to the caecum was removed, after discarding the terminal 20cm. Ileal segments (3cm) were cleaned by passing Krebs-Henseleit buffer containing $3\mu M$ mepyramine gently through the ileum using a Pasteur pipette (size: 13.8cm length, 0.65cm diameter). To avoid unnecessary damage to the tissue, Krebs-Henseleit buffer was passed through the ileal segment, while it was lying horizontally on a petri dish. Therefore, the ileum was not over-distended and the buffer flowed through with ease. Each segment was then passed over a Pasteur pipette and the longitudinal muscle layer and adhering myenteric plexus was teased away using moist cotton wool, by stroking tangentially away from the mesenteric attachment. The tissues were suspended in 20ml organ baths containing Krebs-Henseleit buffer at $37\pm 1^\circ C$ and gassed with 95%CO₂/5%O₂. The tissues were ligated to two parallel stainless steel wires, situated between two platinum electrodes (0.76cm length, 0.06cm diameter). All measurements were recorded isometrically (Grass FTO3 transducer). Following an initial loading tension of 1g, the tissues were stimulated with electrical pulses at a frequency of 0.1Hz and a pulse duration of 0.5msec, as described by Kosterlitz & Watt (*Br. J. Pharmacol.* 1968, 266-276). Initially, the tissues were stimulated at supramaximal (1.3 fold times maximal) voltage for a period of 30 min and then the tissues were washed and re-stimulated. A "sighter dose" of the selective histamine H_3 -receptor agonist, R-(α)-methylhistamine ($0.3\mu M$) (Arrang *et al. Nature*, 1987, 117-123), was administered. Upon generation of response, the "sighter dose" was removed from the tissues by "washout" (6 washes over 60 min) and during this period the electrical stimulation was switched off. The tissues were then re-stimulated and allowed to stabilise prior to the addition of drug treatments, which were allocated on a randomised block basis to the

organ baths. Following the incubation period, a single cumulative E/[A] curve was obtained. The experimental E/[A] curve data was expressed as the percentage inhibition of the peak height of electrically-stimulated contraction. Antagonist affinity values were calculated from the degree of rightward shift of the R-(α)-methylhistamine E/[A] curves using Schild's methods (Arunlakshana & Schild *Br. J. Pharmacol.* 1959, 48-58). Typical variance in this assay is ± 0.15 log units.

The compounds of the invention were also tested in a guinea pig cortex binding assay, as follows:

10

Histamine H₃ radioligand binding assay - guinea pig cortex

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The whole brain was removed and immediately placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at $21 \pm 3^\circ\text{C}$). The cortex was dissected, weighed and homogenised in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at $21 \pm 3^\circ\text{C}$) (50ml/guinea-pig cortex) using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x 3s). The homogenate was centrifuged at 100 x g for 5min and the supernatants pooled and stored at 4°C . The pellets were rehomogenised in fresh ice-cold buffer (80ml) and recentrifuged (100 x g for 5min). The supernatants were pooled and pellets rehomogenised and recentrifuged (100 x g for 5min). All supernatants were pooled and centrifuged at 39,800 x g for 12 min at 4°C . The final pellet was resuspended in 20mM Hepes-NaOH buffer (pH7.4 at $21 \pm 3^\circ\text{C}$) to a tissue concentration of 7.5mg.ml⁻¹, using a teflon-in-glass homogeniser.

25

Incubation conditions

Guinea pig cortex membranes (400 μ l) were incubated for 165 min at $21 \pm 3^\circ\text{C}$ in a final volume of 500 μ l with 20mM Hepes-NaOH buffer containing [³H]-R- α -methylhistamine (50 μ l; 1nM) and competing compound. Total and non-specific binding of [³H]-R- α -methylhistamine were defined using 50 μ l of buffer and 50 μ l of 10 μ M thioperamide, respectively. The assay was terminated by rapid filtration through Whatman GF/B filters, presoaked (2hr) in 0.1% polyethyleneimine, using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH6.9 at $21 \pm 3^\circ\text{C}$),

30

transferred into scintillation vials, 5ml liquid scintillation cocktail was added and after 4 hours the bound radioactivity was determined by counting (4 min) in a Beckman liquid scintillation counter.

5 *Data analysis*

Data are analysed using GraphPad prism and the general equation for a competition curve with variable Hill slope (n_H).

$$Y = \text{Non-specific binding} + \frac{(\text{Total binding} - \text{Non-specific binding})}{1 + 10^{((\log IC_{50} - X) \cdot n_H)}}$$

where

X is the log concentration of competing compound,

Y is the binding obtained at each concentration of X,

pIC_{50} is the concentration of the competitor required to compete for half of the specific binding.

The IC_{50} is converted to the K_i using the Cheng Prusoff equation,

$$K_i = IC_{50} / (1 + (L/K_D))$$

where

IC_{50} is the concentration of competitor required to compete for half the specific binding,

L is the radioligand concentration used,

K_D is the equilibrium dissociation constant for the radioligand determined by saturation experiments.

The results obtained from the functional and binding assays described above are set out in the Table below:

Table

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
1	7.2	5.4
2	7.3	6.4

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
3	7.1	6.1
4	7.1	6.5
5	7.0	6.1
6	7.3	6.4
7	7.4	6.4
8	7.7	6.2
9	8.3	6.5
10	7.6	6.5
11	7.4	6.3
12	6.2	6.3
13	7.7	6.3
14	7.6	6.0
15	6.1	NT
16	6.2	5.4
17	8.3	7.3
18	8.3	7.3
19	7.3	6.0
20	9.0	6.7
21	7.3	6.8
22	7.1	6.7
23	6.5	5.5
24	8.2	6.2
25	8.1	7.1
26	7.4	6.8
27	6.8	NT
28	7.5	6.7
29	8.4	7.7
30	8.5	7.9
31	8.4	8.0
32	8.5	8.0
33	7.1	6.7

Example	pK _i (Guinea pig cortex)	pK _b (Guinea pig ileum)
34	6.5	6.5
35	8.1	7.7
36	7.3	7.2
37	7.9	7.6
38	7.5	7.2
39	7.4	NT
40	8.4	7.4
41	8.9	7.5
42	7.6	6.4
43	7.0	6.7
44	8.8	7.6
45	8.4	7.5
46	8.5	7.7
47	8.4	7.3
48	8.5	7.6
49	8.2	7.5
50	7.8	6.5
51	8.1	7.0
52	6.5	6.5
53	8.1	7.1
54	7.3	7.1
55	7.5	6.6
56	7.7	7.2
57	7.7	NT
58	8.5	6.7
59	8.0	7.0
60	8.0	8.1
61	8.1	7.8
62	7.5	7.4
63	7.7	7.4
64	7.2	6.2

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
65	8.3	7.1
66	8.6	7.4
67	8.6	7.3
68	8.1	7.3
69	9.0	7.9
70	8.3	8.4
71	8.7	8.4
72	8.3	8.5
73	8.8	7.8
74	8.1	7.9
75	7.6	6.9
76	8.8	8.1
77	8.2	8.0
78	7.1	7.5
79		8.1
80		8.0
81	6.9	5.9
82	6.5	6.0
83	6.6	6.2
84	6.3	6.1
85	6.8	NT
86	5.6	NT
87	5.9	NT
88	6.2	5.9
89	7.0	6.2
90	5.9	NT
91	6.9	6.3
92	5.7	NT
93	5.5	NT
94	5.6	NT
95	5.8	NT

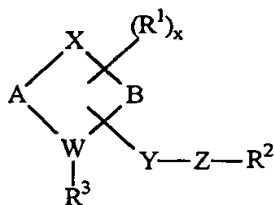
Example	pK _i (Guinea pig cortex)	pK _b (Guinea pig ileum)
96	5.8	NT
97	5.8	5.5
98	6.1	6.1
99	6.7	6.5
100	6.7	6.3
101	6.6	6.0
102	7.2	6.5
103	6.9	6.5
104	6.4	6.4
105	6.4	6.3
106	6.0	6.2
107	7.0	6.8
108	5.8	NT
109	6.7	NT
110	6.3	5.6
111	5.8	NT
112	6.4	5.8
113	7.0	6.7
114	6.5	7.0
115	6.3	6.4
116	6.9	6.7
117	7.1	NT
118	5.8	NT
119	7.8	5.7
120	6.3	6.3
121	6.5	6.0
122	6.9	6.5
123	6.6	5.5
124	5.9	NT
125	6.5	<5.5
126	6.0	5.5

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
127	5.7	5.7
128	5.5	NT
129	6.1	NT
130	5.3	NT
131	6.0	<5.5
132	6.9	5.8
133	5.6	<5.5
134	6.0	NT
135	6.5	6.2
136	6.5	6.5
137	5.6	NT
138	5.9	NT
139	6.7	6.3
140	8.1	6.5
141	6.6	6.3
142	6.2	5.7
143	6.1	5.5

NT= not tested

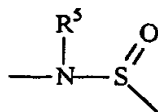
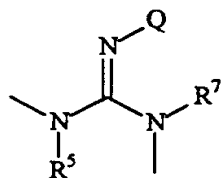
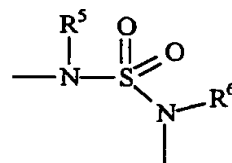
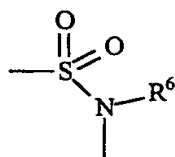
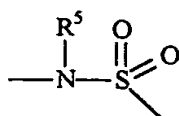
CLAIMS

1. A compound of the formula

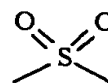


wherein

- 5 A is $(CH_2)_m$, m being from 1 to 3;
 B is $(CH_2)_n$, n being from 1 to 3;
 x is from 0 to 2;
 R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by
 O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;
 10 R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be
 replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by
 halogen;
 R^3 is absent when $-Y-Z-R^2$ is attached to W, or is H or C_1 to C_7 hydrocarbyl
 when $-Y-Z-R^2$ is not attached to W;
 15 W is nitrogen;
 X is $-CH_2-$, $-O-$ or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;
 Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10}
 alkylene, in which one non-terminal carbon atom may be replaced by
 O; and
 20 Z is



or



wherein R^5 , R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which
 up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen

atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R⁵ or R⁷ to form a five-membered ring or Q is linked to R² to form a six-membered ring,

or a pharmaceutically acceptable salt thereof.

5

2. A compound according to claim 1 wherein R² is selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C₁ to C₄ alkyl, C₁ to C₄ alkoxy or halo.

10

3. A compound according to claim 1 wherein R² is selected from phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, 15 adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

4. A compound according to any of claims 1 to 3 wherein x is 0.

20 5. A compound according to any of claims 1 to 3 wherein x is 1 or 2, and R¹ is selected from hydroxy, C₁ to C₉ alkoxy (optionally substituted by halo), C₁ to C₉ cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C₁ to C₄ alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C₁ to C₄ alkyl, C₁ to C₃ alkoxy or halo, and the 25 alkoxy group is optionally substituted by halo) and C₁ to C₉ alkylamino wherein the alkyl group is optionally substituted by halo.

6. A compound according to any preceding claim wherein R³ is H, C₁ to C₇ alkyl or benzyl

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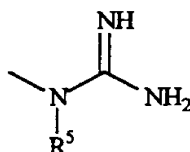
7. A compound according to any preceding claim wherein R⁵, R⁶ and R⁷ are independently selected from H, aryl(C₁ to C₃)alkyl and cycloalkyl(C₁ to C₃)alkyl, and are optionally substituted by halo.

8. A compound according to any preceding claim wherein Y is propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene.

9. A compound according to any preceding claim wherein $m+n \geq 3$.

5

10. A compound according to claim 8, wherein $m+n \geq 3$, Z-R² is



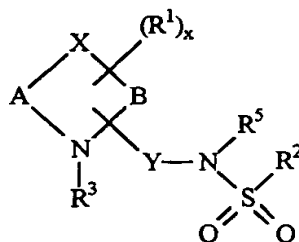
and R⁵ is benzyl or halobenzyl.

10 11. A compound according to any preceding claim, for use in therapy.

12. A compound which is degraded *in vivo* to yield a compound according to any of claims 1 to 10.

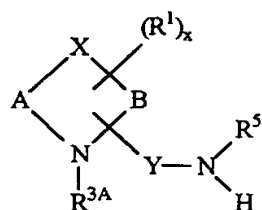
15 13. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 10, and a physiologically acceptable diluent or carrier.

14. A method of making a compound of the formula



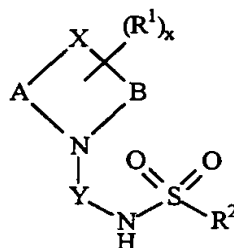
20

wherein A, B, x, R¹, R², R³, R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula R²SO₂Cl with a compound of the formula



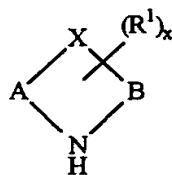
wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group.

15. A method of making a compound of the formula



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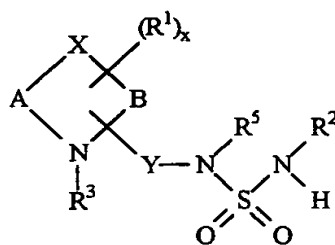
wherein A, B, x , R^1 , R^2 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



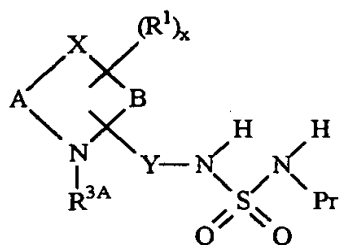
with a compound of the formula $Cl-Y-NH-SO_2-R^2$.

10

16. A method of making a compound of the formula



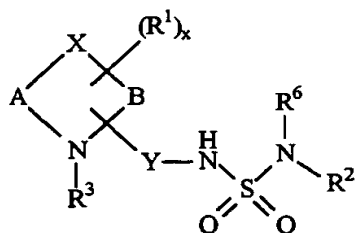
wherein A, B, x , R^1 , R^2 , R^3 , R^5 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



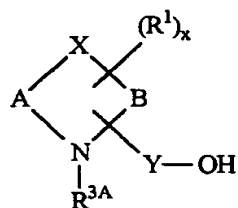
(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group and Pr is a protecting group) with a compound of the formula R^2Br , and reacting the product with R^5Br when R^5 is not hydrogen.

5

17. A method of making a compound of the formula



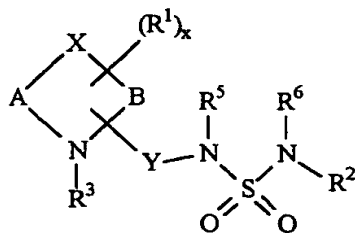
wherein A, B, x, R^1 , R^2 , R^3 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



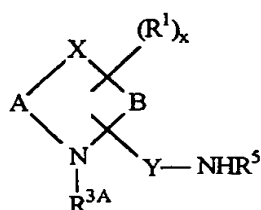
10

(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula $R^2-NH-SO_2-NH-Pr$, wherein Pr is a protecting group, and reacting the product with R^6Br when R^6 is not hydrogen.

15 18. A method of making a compound of the formula

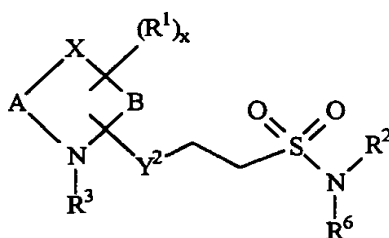


wherein A, B, x, R^1 , R^2 , R^3 , R^5 , R^6 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

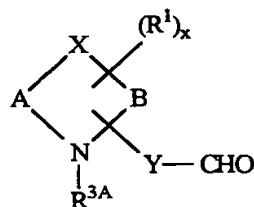


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2R^6NH and sulfamide.

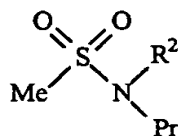
- 5 19. A method of making a compound of the formula



wherein A, B, x, R^1 , R^2 , R^3 , R^6 and X are as recited in claim 1 and Y^2 is a bond or C_1 to C_8 alkylene, said method comprising the step of reacting a compound of the formula



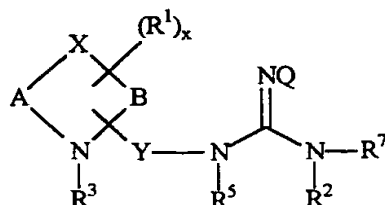
- 10 (wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula



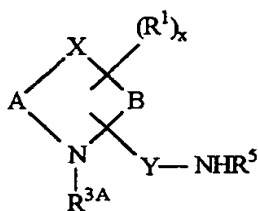
wherein Pr is a protecting group, reducing the reaction product, and (when R^6 is not hydrogen) reacting the reduced product with R^6Br .

15

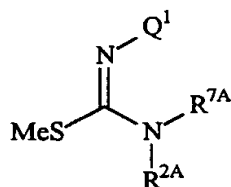
20. A method of making a compound of the formula



wherein A, B, x, R¹, R², R³, R⁵, R⁷, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



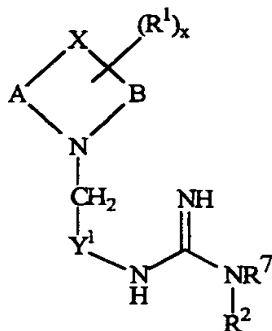
with a compound of the formula



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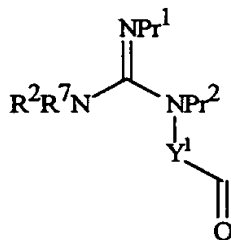
wherein Q¹, R^{2A}, R^{3A}, and R^{7A} are any of the groups defined for Q, R², R³, and R⁷, respectively, or protecting groups.

21. A method of making a compound of the formula

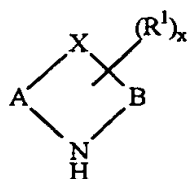


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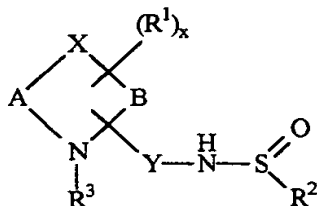
wherein A, B, x, R¹, R², and X are as recited in claim 1 and Y¹ is a C₁ to C₉ alkylene group, said method comprising the step of reacting a compound of the formula



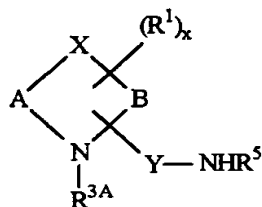
(wherein Pr¹ and Pr² are protecting groups) with a compound of the formula



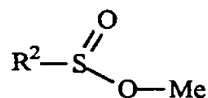
22. A method of making a compound of the formula



5 wherein A, B, x, R¹, R², R³, R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

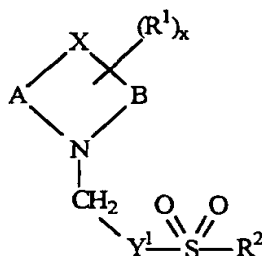


(wherein R^{3A} is C₁ to C₇ hydrocarbyl or a protecting group) with a compound of the formula

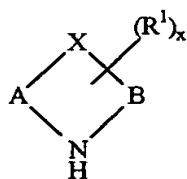


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23. A method of making a compound of the formula

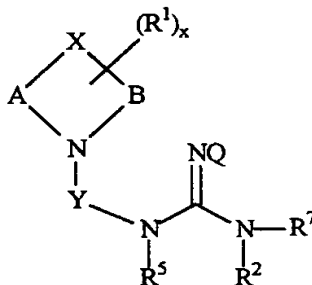


15 wherein A, B, x, R¹, R², and X are as recited in claim 1 and Y¹ is a C₁ to C₉ alkylene group, said method comprising the step of reacting a compound of the formula



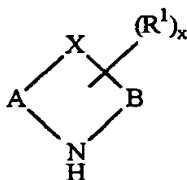
with a compound of the formula $R^2-SO_2-Y^1-CHO$.

24. A method of making a compound of the formula

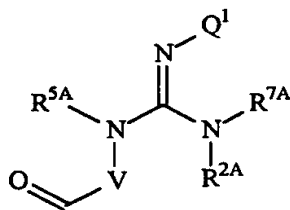


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wherein A, B, x, R^1 , R^2 , R^5 , R^7 , Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



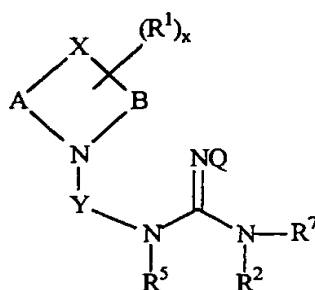
with a compound of the formula



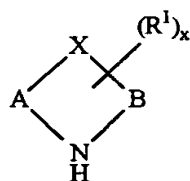
10

wherein V is C_1 to C_9 alkylene, and Q^1 , R^{2A} , R^{5A} and R^{7A} are any of the groups defined for Q, R^2 , R^5 and R^7 , respectively, or a protecting group.

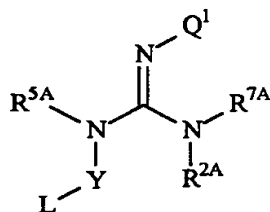
25. A method of making a compound of the formula



wherein A, B, x, R¹, R², R⁵, R⁷, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

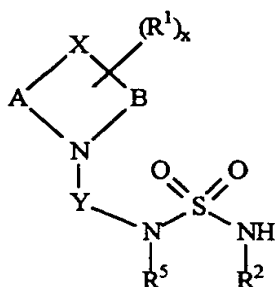


5 with a compound of the formula

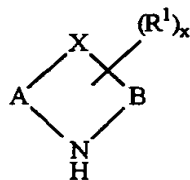


wherein L is a leaving group, and Q¹, R^{2A}, R^{5A} and R^{7A} are any of the groups defined for Q, R², R⁵ and R⁷, respectively, or a protecting group.

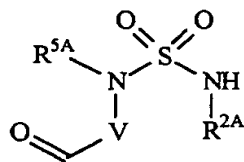
10 26. A method of making a compound of the formula



wherein A, B, x, R¹, R², R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



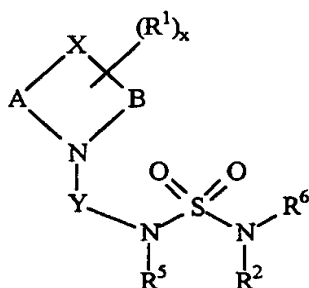
with a compound of the formula



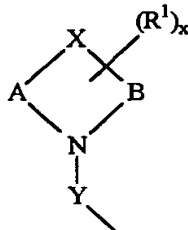
wherein V is C₁ to C₉ alkylene, and R^{2A} and R^{5A} are any of the groups recited for R² and R⁵, respectively, or a protecting group.

5

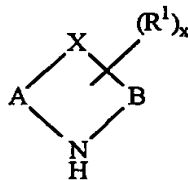
27. A method of making a compound of the formula



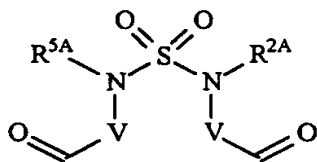
wherein A, B, x, R¹, R², R⁵, X and Y are as recited in claim 1 (provided that the moiety



10 constitutes a group falling within the definition of R⁶), said method comprising the step of reacting a compound of the formula



with a compound of the formula



15 wherein V is C₁ to C₉ alkylene, and R^{2A} and R^{5A} are any of the groups recited for R² and R⁵, respectively, or a protecting group.

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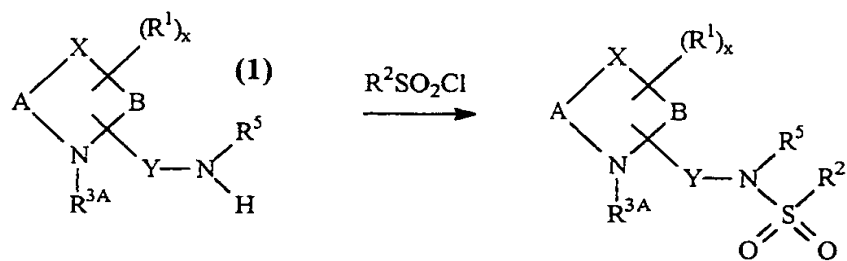


Figure 1

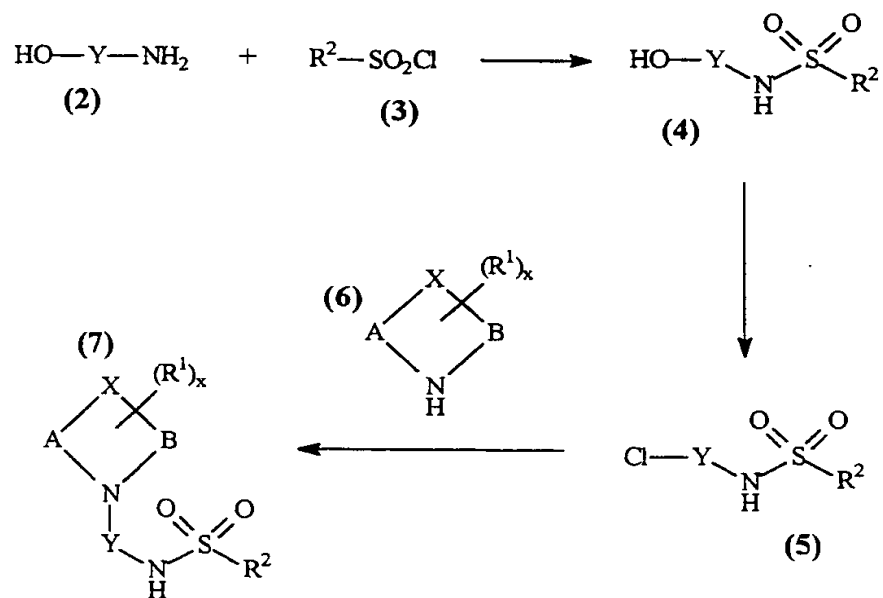


Figure 2

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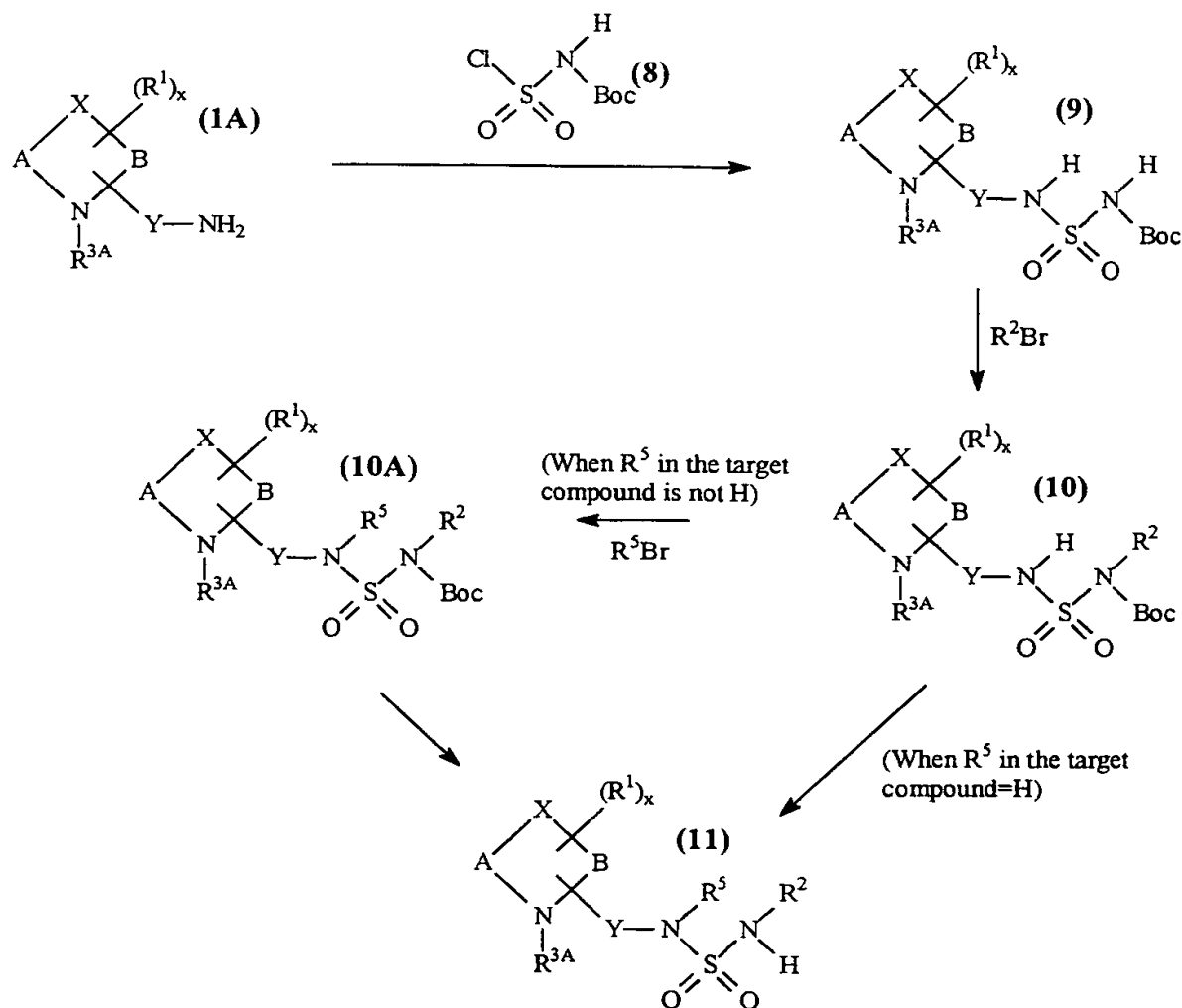


Figure 3

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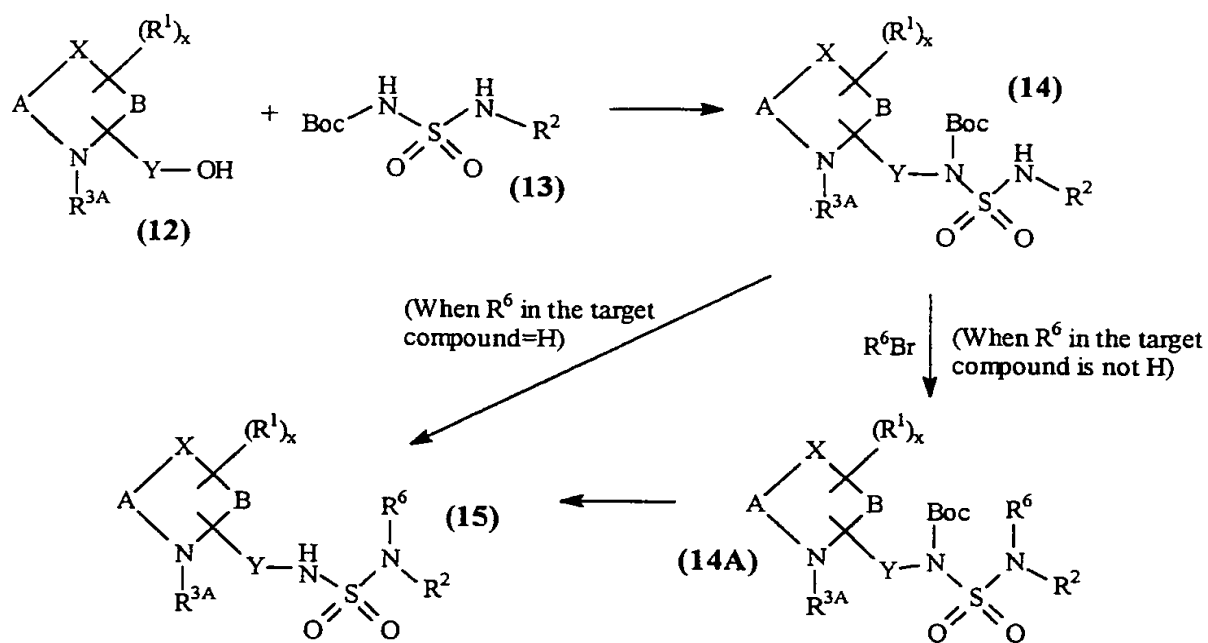


Figure 4

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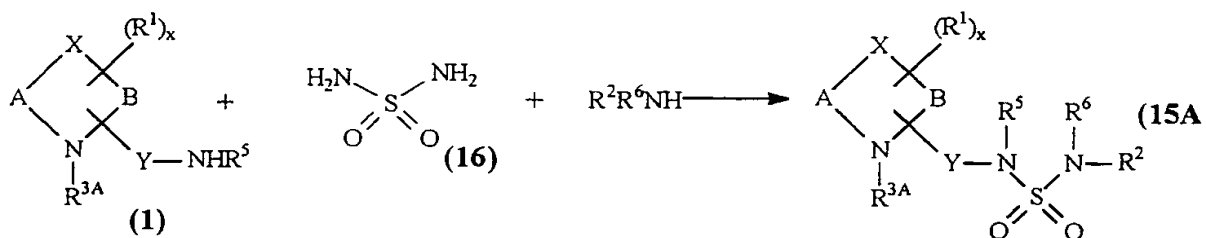


Figure 5

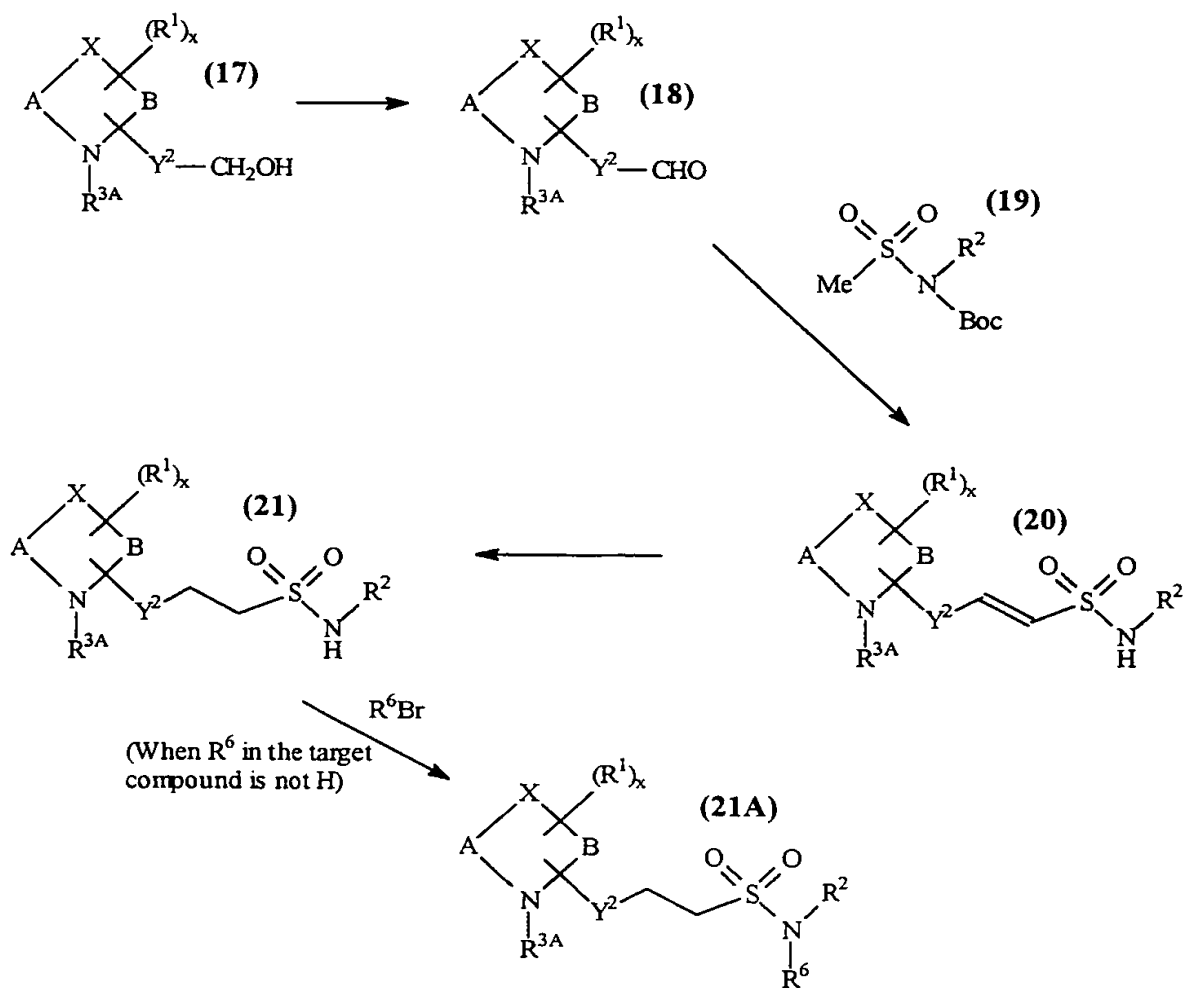


Figure 6

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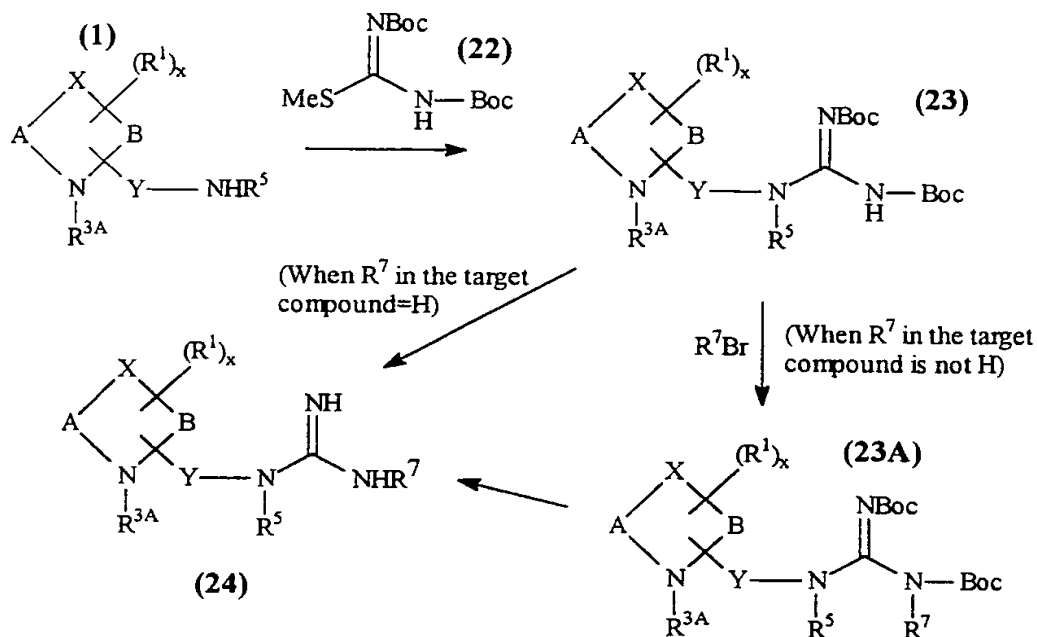


Figure 7

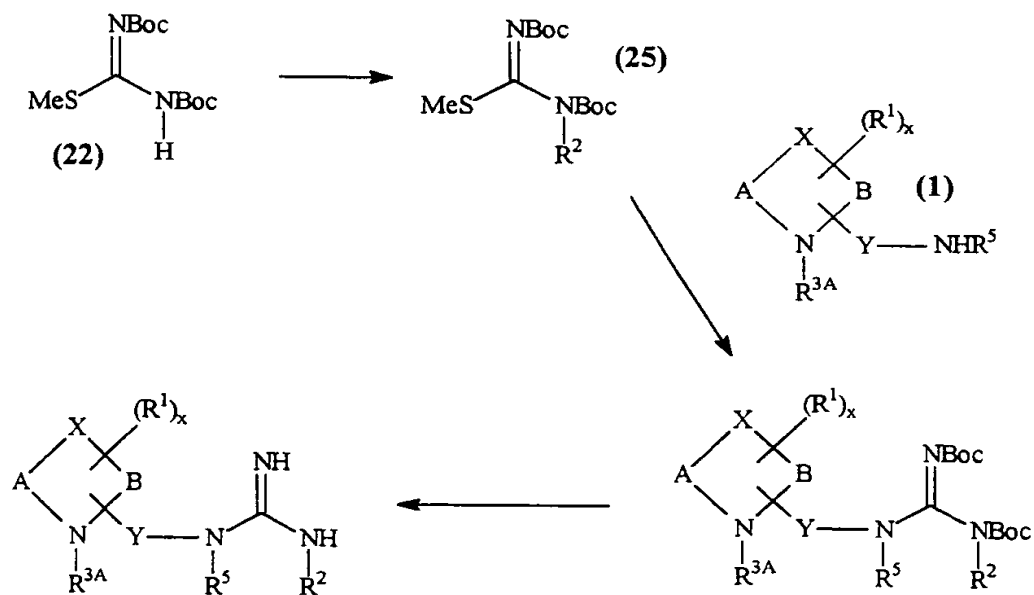


Figure 8

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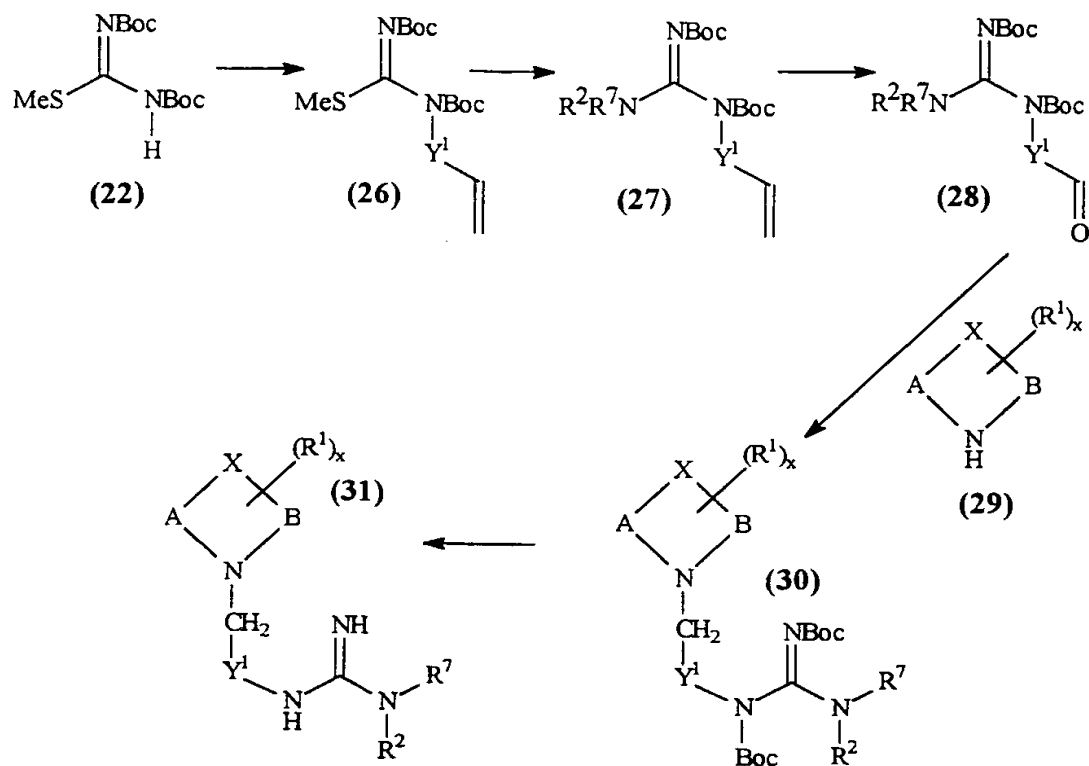


Figure 9

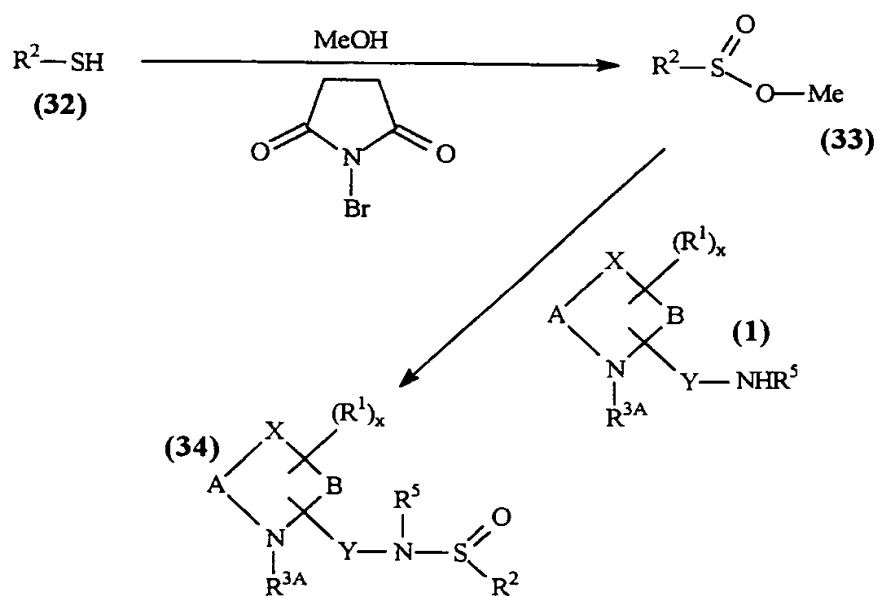


Figure 10

7/11

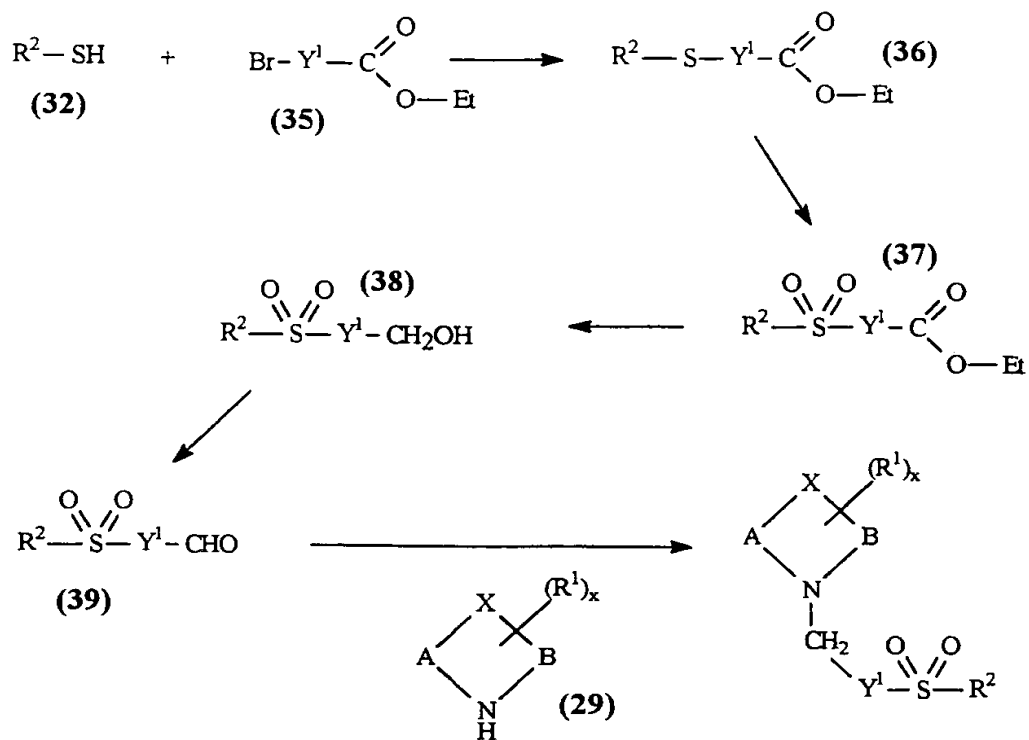


Figure 11

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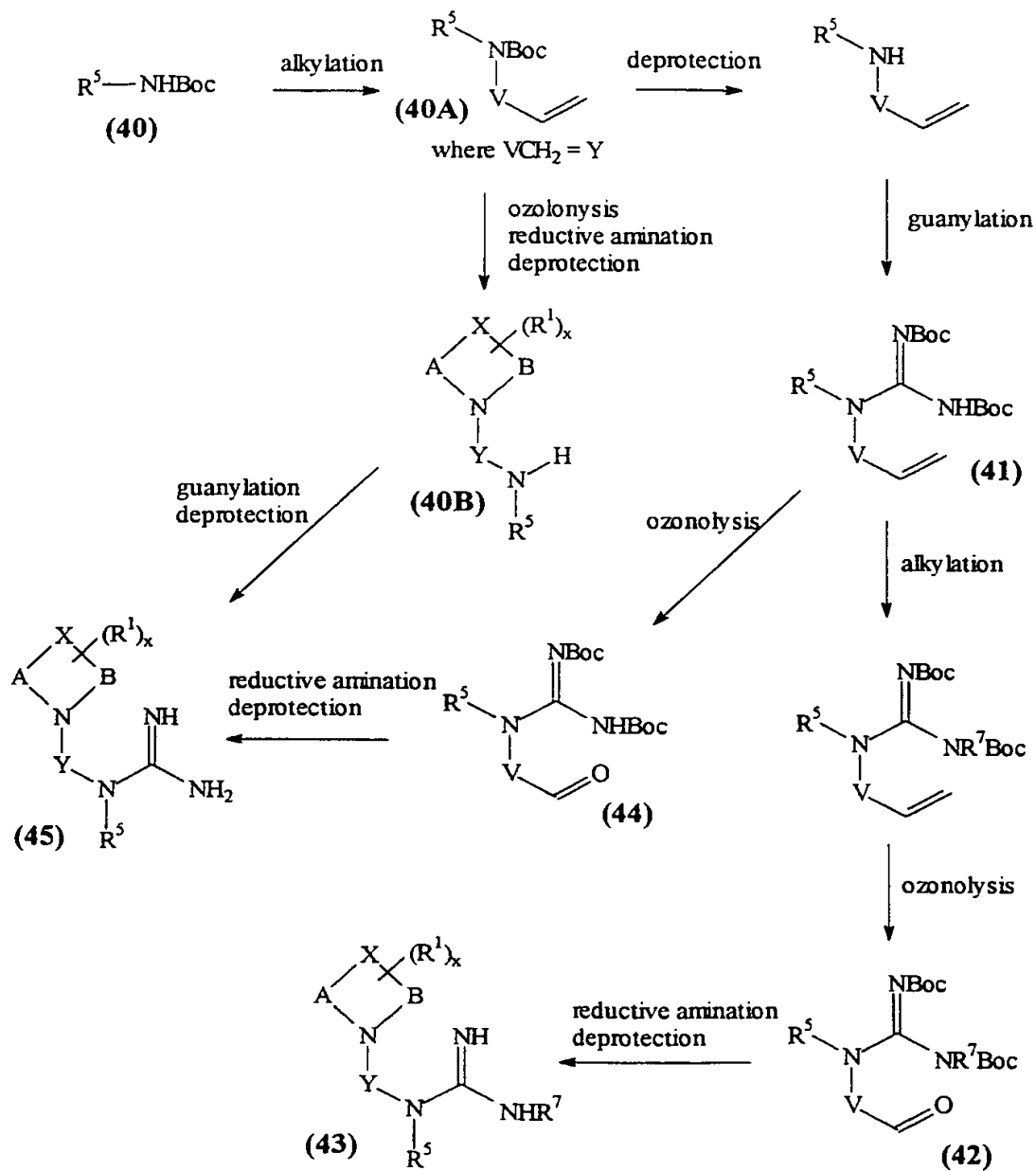


Figure 12

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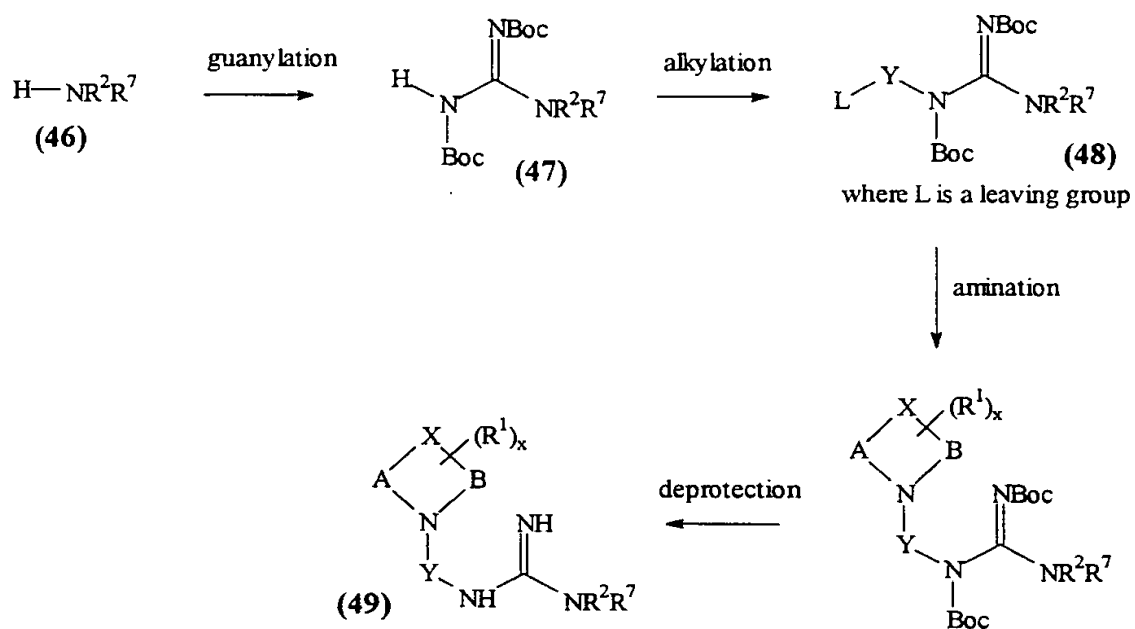


Figure 13

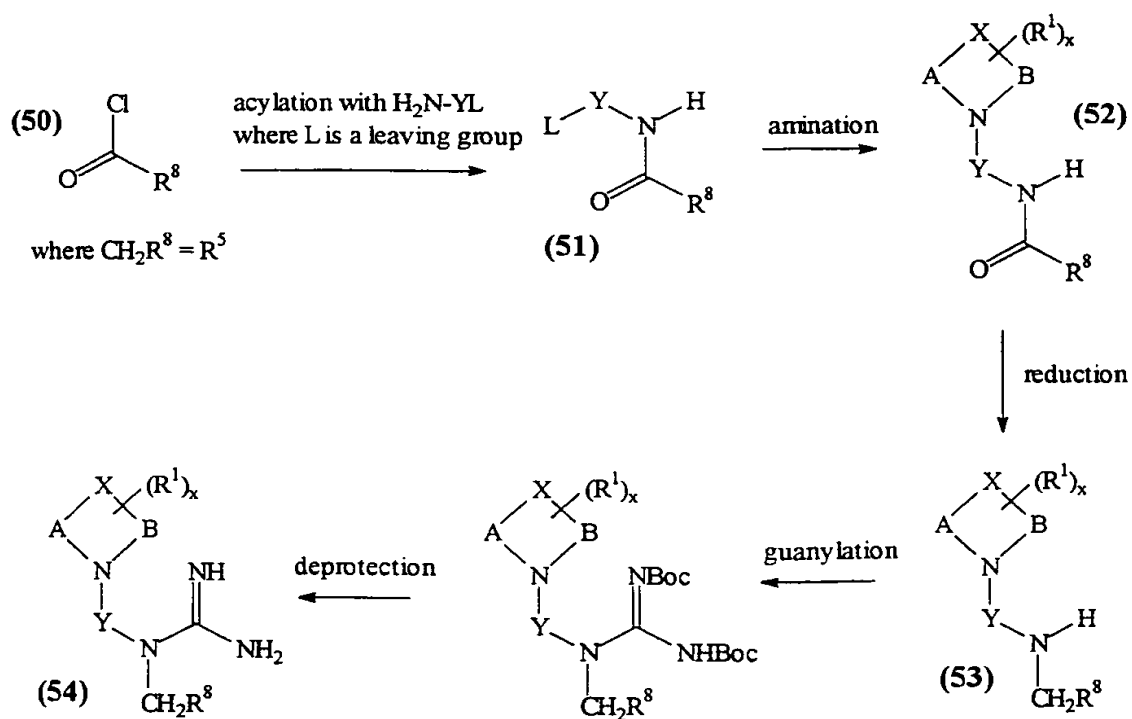


Figure 14

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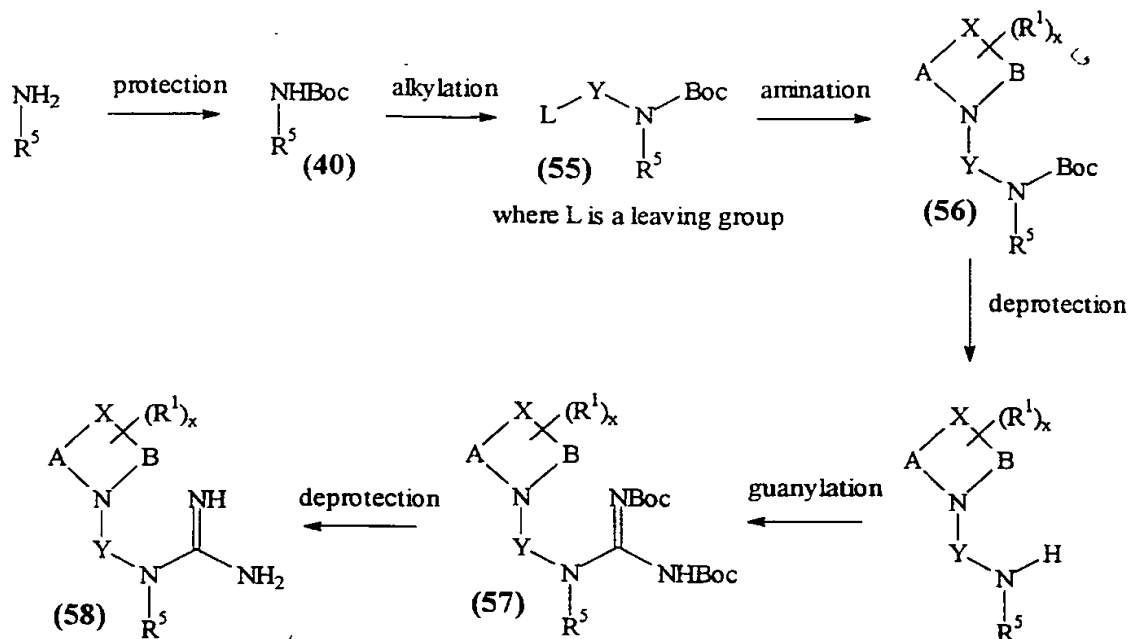


Figure 15

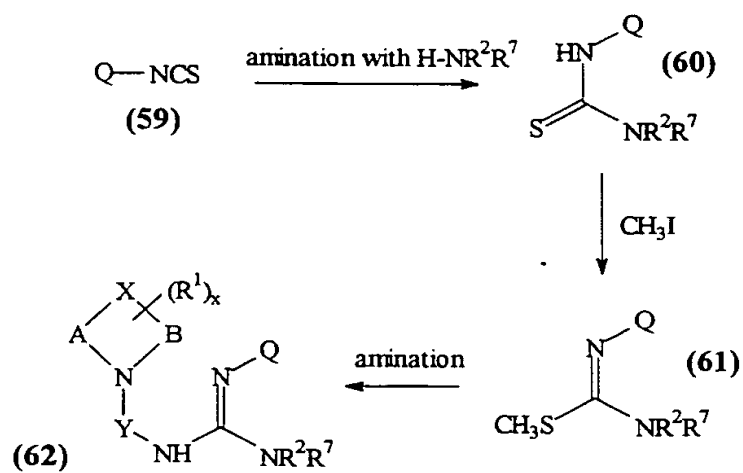


Figure 16

11/11

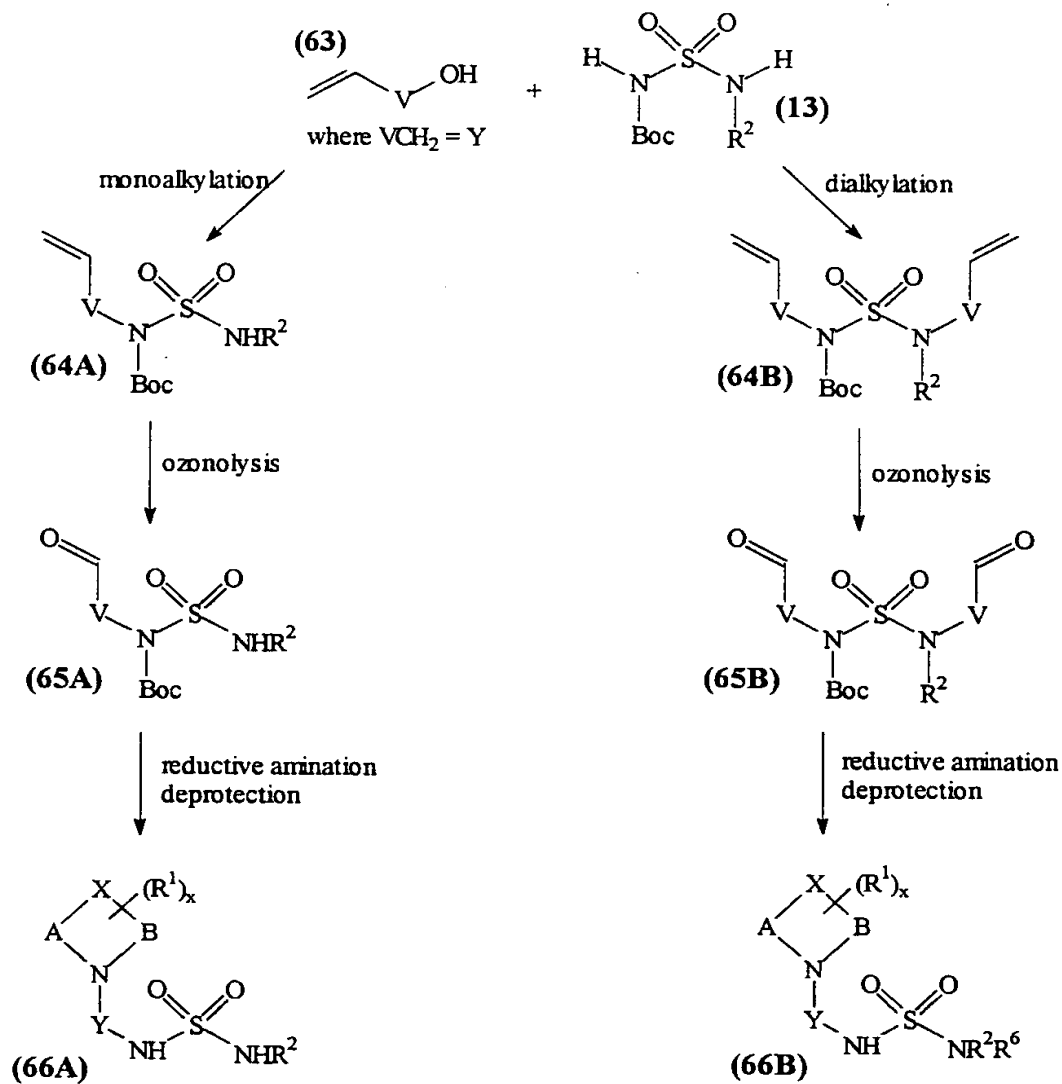


Figure 17

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00464

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/12 A61K31/395 C07D207/08 C07D403/06 C07D401/12
C07D405/12 C07D295/08 C07D403/12 C07D211/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CH 390 925 A (CIBA AG) * example 1-4; page 9, compounds d), e) and g); page 3, line 66-75 *	1, 13
X	CH 390 926 A (CIBA AG) * page 3, line 65-77; page 6, right column *	1, 13
X	CH 390 927 A (CIBA AG) * page 3, line 6-18; page 6 and 7 *	1, 13
X	CH 390 928 A (CIBA AG) * page 3, line 66-78; page 6 and 7 *	1, 13
X	CH 342 957 A (CIBA AG) see page 2	1, 13
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 May 1999

Date of mailing of the international search report

25/05/1999

Name and mailing address of the ISA

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Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00464

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CH 345 893 A (CIBA AG) see page 2 - page 4 ---	1, 13
X	CH 346 879 A (CIBA AG) see page 2 ---	1, 13
X	CH 362 079 A (CIBA AG) see page 3 ---	1, 13
X	CH 393 337 A (CIBA AG) * example 1-3, 20:25, 30, 31 * ---	1, 13
X	GB 952 194 A (SMITH KLINE & FRENCH LABORATORIES LTD.) see claims ---	1, 13
X	FR 1 352 161 A (SOCIETA FARMACEUTICI ITALIA) 15 May 1964 see page 1 ---	1, 13
X	GB 1 185 080 A (BEECHAM GROUP LTD) 18 March 1970 see claims ---	1, 13
X	CH 442 298 A (F. HOFFMANN-LA ROCHE & CO.) see claims ---	1, 13
A	WO 97 29092 A (JAMES BLACK FOUNDATION LTD) 14 August 1997 see page 2, line 12 - line 13; claim 1 ---	1, 13
A	WO 93 14070 A (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE) 22 July 1993 cited in the application see claims 1, 28 ---	1, 13
A	WO 92 15567 A (SEED CAPITAL INVESTMENT (SCI) B.V.) 17 September 1992 cited in the application see claims 1, 19 -----	1, 13

INTERNATIONAL SEARCH REPORT

national application No.

PCT/GB 99/00464

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the broad Markush claims , the search was executed with due regard to PCT Search Guidelines (PCT/GL2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, histamine H3 receptor ligands of the general formula of claim 1

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/GB 99/00464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 390925 A		NONE	
CH 390926 A		NONE	
CH 390927 A		NONE	
CH 390928 A		NONE	
CH 342957 A		NONE	
CH 345893 A		NONE	
CH 346879 A		NONE	
CH 362079 A		NONE	
CH 393337 A		FR 1299505 A NL 251629 A	07-12-1962
GB 952194 A		US 3283003 A	01-11-1966
FR 1352161 A	15-05-1964	NONE	
GB 1185080 A	18-03-1970	AT 301569 B BE 725104 A CH 533105 A CH 534679 A DE 1811832 A DK 126781 B ES 361114 A FR 7874 M IE 32781 B NL 6817322 A SE 346785 B ZM 17068 A	15-08-1972 06-06-1969 31-01-1973 15-03-1973 03-07-1969 20-08-1973 01-08-1970 27-04-1970 28-11-1973 10-06-1969 17-07-1972 17-06-1969
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WO 9729092 A	14-08-1997	AU 1613697 A CA 2244745 A EP 0882023 A NO 983596 A PL 328369 A	28-08-1997 14-08-1997 09-12-1998 16-09-1998 18-01-1999
WO 9314070 A	22-07-1993	FR 2686084 A CA 2105867 A EP 0597088 A JP 6506003 T US 5559113 A US 5708171 A	16-07-1993 11-07-1993 18-05-1994 07-07-1994 24-09-1996 13-01-1998
WO 9215567 A	17-09-1992	NL 9100365 A	16-09-1992

INTERNATIONAL SEARCH REPORT

information on patent family members

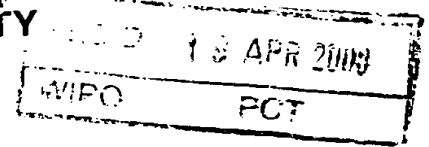
International Application No

PCT/GB 99/00464

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9215567 A		AT 159248 T	15-11-1997
		AU 662135 B	24-08-1995
		AU 1541892 A	06-10-1992
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		DE 69222757 D	20-11-1997
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		DK 573542 T	18-05-1998
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		GR 3025554 T	31-03-1998
		JP 6505265 T	16-06-1994
		NL 9101764 A	16-09-1992

PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P018722WO.AJF	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/00464	International filing date (day/month/year) 15/02/1999	Priority date (day/month/year) 19/02/1998
International Patent Classification (IPC) or national classification and IPC C07D295/12		
Applicant JAMES BLACK FOUNDATION LIMITED et al.		



1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/09/1999	Date of completion of this report 14. 04. 00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mathys, E Telephone No. +49 89 2399 8596 

ITEM V

Novelty

The documents cited in the search report under Category X do not disclose heterocycles containing a moiety Z as defined in claim 1 or compounds useful as H₃ receptor.

The present compounds differ from histamine H₃ receptors disclosed by (D1) WO-A- 97/29092, (D2) WO-A-93/14070 and (D3) WO-A-92/15567 in having a saturated heterocycle in the place of an imidazole moiety.

Inventive Step

From the combined state of the art D1 to D3 it had to be expected that the presence of an imidazole ring would be essential for the property as histamine H₃ receptor, also in view of the fact that histamine itself includes an imidazole ring.

ITEM VII

The description is not in conformity with the claims.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00464

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-92 as originally filed

Claims, No.:

1-28 as received on 29/02/2000 with letter of 28/02/2000

Drawings, sheets:

1/11-11/11 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/00464

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-28
	No: Claims
Inventive step (IS)	Yes: Claims 1-28
	No: Claims
Industrial applicability (IA)	Yes: Claims 1-28
	No: Claims

2. Citations and explanations

see separate sheet

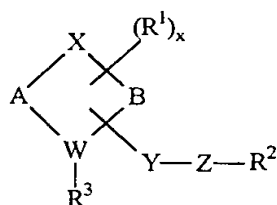
VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

CLAIMS

1. A compound of the formula



wherein

5 A is $(\text{CH}_2)_m$, m being from 1 to 3;

B is $(\text{CH}_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

10 R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

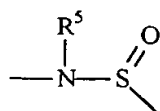
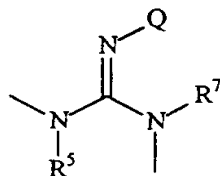
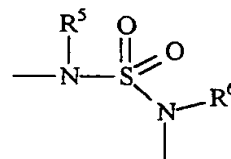
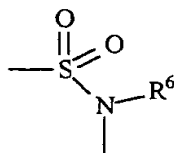
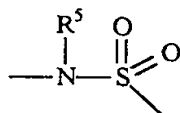
R^3 is absent when $-\text{Y}-\text{Z}-\text{R}^2$ is attached to W, or is H or C_1 to C_7 hydrocarbyl when $-\text{Y}-\text{Z}-\text{R}^2$ is not attached to W;

15 W is nitrogen;

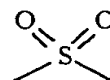
X is $-\text{CH}_2-$, $-\text{O}-$ or $-\text{NR}^4-$, R^4 being H or C_1 to C_3 alkyl;

Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10} alkylene, in which one non-terminal carbon atom may be replaced by O; and

20 Z is



or



wherein R^5 , R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen

atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R⁵ or R⁷ to form a five-membered ring or Q is linked to R² to form a six-membered ring,

or a pharmaceutically acceptable salt thereof.

5

2. A compound according to claim 1 wherein R² is selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C₁ to C₄ alkyl, C₁ to C₄ alkoxy or halo.

10

3. A compound according to claim 1 wherein R² is selected from phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

15

4. A compound according to any of claims 1 to 3 wherein x is 0.

20 5. A compound according to any of claims 1 to 3 wherein x is 1 or 2, and R¹ is selected from hydroxy, C₁ to C₉ alkoxy (optionally substituted by halo), C₁ to C₉ cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C₁ to C₄ alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C₁ to C₄ alkyl, C₁ to C₃ alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C₁ to C₉ alkylamino wherein the alkyl group is optionally substituted by halo.

25

6. A compound according to any preceding claim wherein R³ is H, C₁ to C₇ alkyl or benzyl

30

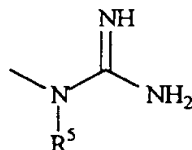
7. A compound according to any preceding claim wherein R⁵, R⁶ and R⁷ are independently selected from H, aryl(C₁ to C₃)alkyl and cycloalkyl(C₁ to C₃)alkyl, and are optionally substituted by halo.

8. A compound according to any preceding claim wherein Y is propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene.

9. A compound according to any preceding claim wherein $m+n \geq 3$.

5

10. A compound according to claim 8, wherein $m+n \geq 3$, Z-R² is



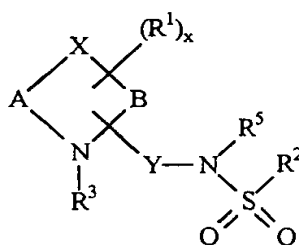
and R⁵ is benzyl or halobenzyl.

10 11. A compound according to any preceding claim, for use in therapy.

12. A compound which is degraded *in vivo* to yield a compound according to any of claims 1 to 10.

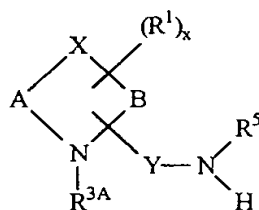
15 13. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 10, and a physiologically acceptable diluent or carrier.

14. A method of making a compound of the formula



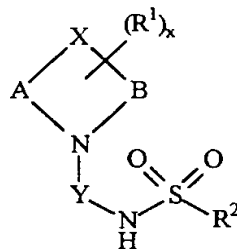
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wherein A, B, x, R¹, R², R³, R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula R²SO₂Cl with a compound of the formula



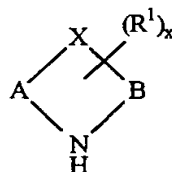
wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group.

15. A method of making a compound of the formula



5

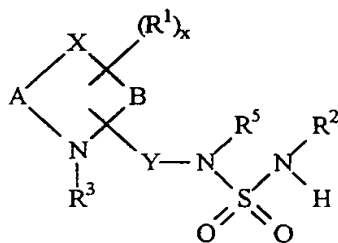
wherein A, B, x, R^1 , R^2 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



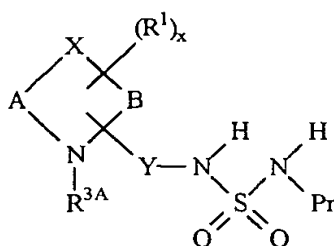
with a compound of the formula $Cl-Y-NH-SO_2-R^2$.

10

16. A method of making a compound of the formula



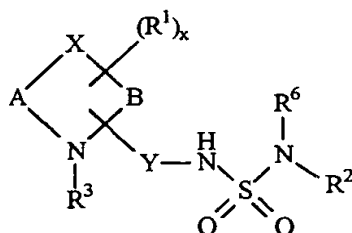
wherein A, B, x, R^1 , R^2 , R^3 , R^5 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



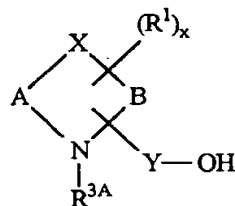
(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group and Pr is a protecting group) with a compound of the formula R^2Br , and reacting the product with R^5Br when R^5 is not hydrogen.

5

17. A method of making a compound of the formula



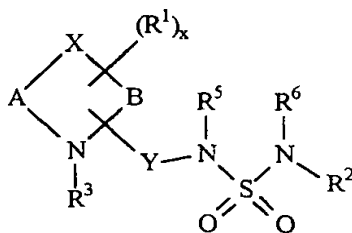
wherein A, B, x, R^1 , R^2 , R^3 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



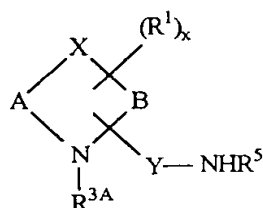
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(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula $R^2-NH-SO_2-NH-Pr$, wherein Pr is a protecting group, and reacting the product with R^6Br when R^6 is not hydrogen.

15 18. A method of making a compound of the formula

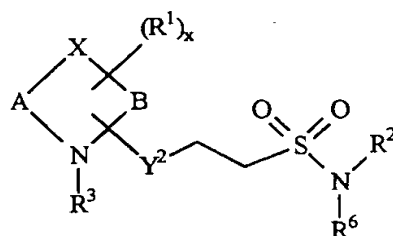


wherein A, B, x, R^1 , R^2 , R^3 , R^5 , R^6 , X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

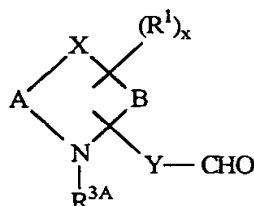


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2R^6NH and sulfamide.

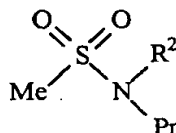
- 5 19. A method of making a compound of the formula



wherein A, B, x, R^1 , R^2 , R^3 , R^6 and X are as recited in claim 1 and Y^2 is a bond or C_1 to C_8 alkylene, said method comprising the step of reacting a compound of the formula



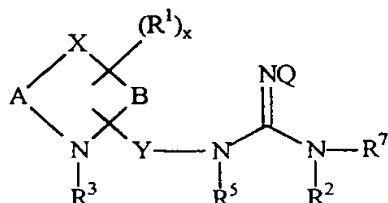
- 10 (wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula



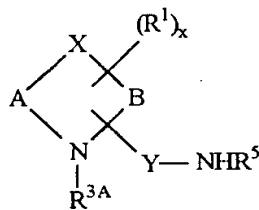
wherein Pr is a protecting group, reducing the reaction product, and (when R^6 is not hydrogen) reacting the reduced product with R^6Br .

15

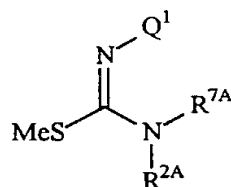
20. A method of making a compound of the formula



wherein A, B, x, R¹, R², R³, R⁵, R⁷, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



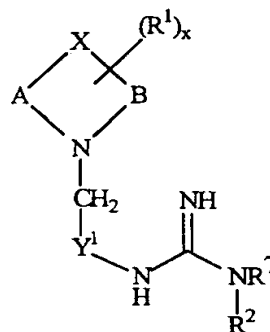
with a compound of the formula



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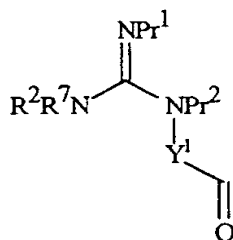
wherein Q¹, R^{2A}, R^{3A}, and R^{7A} are any of the groups defined for Q, R², R³, and R⁷, respectively, or protecting groups.

21. A method of making a compound of the formula

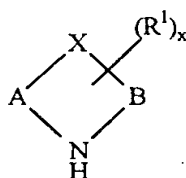


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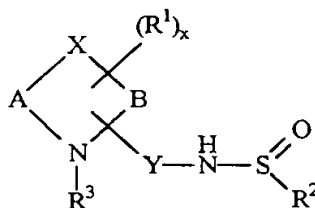
wherein A, B, x, R¹, R², and X are as recited in claim 1 and Y¹ is a C₁ to C₉ alkylene group, said method comprising the step of reacting a compound of the formula



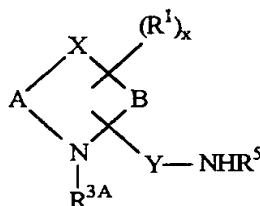
(wherein Pr¹ and Pr² are protecting groups) with a compound of the formula



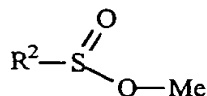
22. A method of making a compound of the formula



5 wherein A, B, x, R¹, R², R³, R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

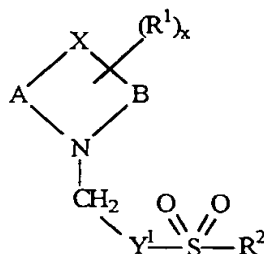


(wherein R^{3A} is C₁ to C₇ hydrocarbonyl or a protecting group) with a compound of the formula



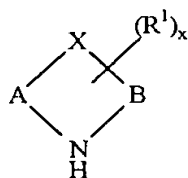
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23. A method of making a compound of the formula



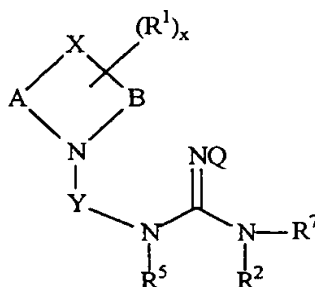
wherein A, B, x, R¹, R², and X are as recited in claim 1 and Y¹ is a C₁ to C₉ alkylene

15 group, said method comprising the step of reacting a compound of the formula



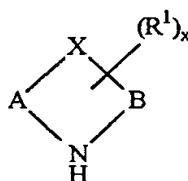
with a compound of the formula $R^2-SO_2-Y^1-CHO$.

24. A method of making a compound of the formula

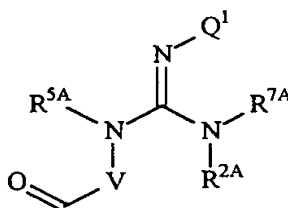


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wherein A, B, x, R^1 , R^2 , R^5 , R^7 , Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



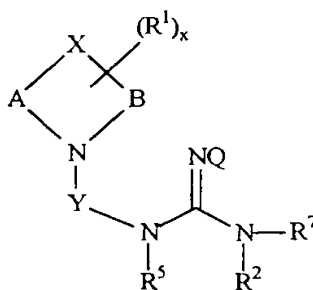
with a compound of the formula



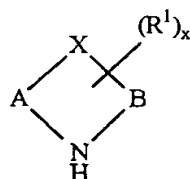
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wherein V is C_1 to C_9 alkylene, and Q^1 , R^{2A} , R^{5A} and R^{7A} are any of the groups defined for Q, R^2 , R^5 and R^7 , respectively, or a protecting group.

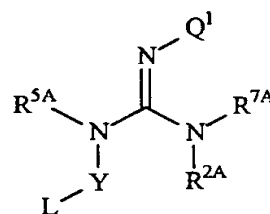
25. A method of making a compound of the formula



wherein A, B, x, R¹, R², R⁵, R⁷, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

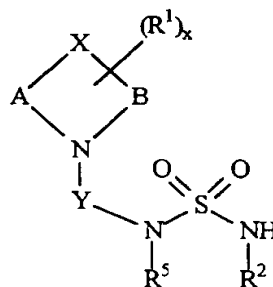


5 with a compound of the formula

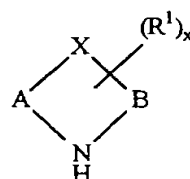


wherein L is a leaving group, and Q¹, R^{2A}, R^{5A} and R^{7A} are any of the groups defined for Q, R², R⁵ and R⁷, respectively, or a protecting group.

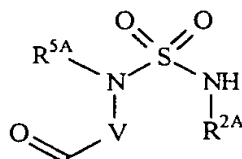
10 26. A method of making a compound of the formula



wherein A, B, x, R¹, R², R⁵, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



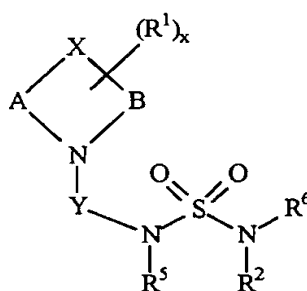
with a compound of the formula



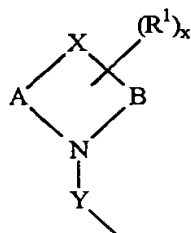
wherein V is C₁ to C₉ alkylene, and R^{2A} and R^{5A} are any of the groups recited for R² and R⁵, respectively, or a protecting group.

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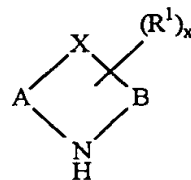
27. A method of making a compound of the formula



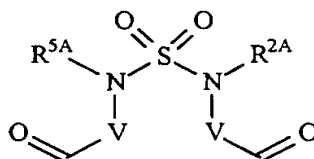
wherein A, B, x, R¹, R², R⁵, X and Y are as recited in claim 1 (provided that the moiety



10 constitutes a group falling within the definition of R⁶), said method comprising the step of reacting a compound of the formula



with a compound of the formula



15 wherein V is C₁ to C₉ alkylene, and R^{2A} and R^{5A} are any of the groups recited for R² and R⁵, respectively, or a protecting group.